**Thesis Project Portfolio**

# Differences in cellular responses using microporous annealed particle (MAP) hydrogels with varied chemical compositions

(Technical Report)

# Analysis of how self-image is generated through the use of cosmetic surgery

(STS Research Paper)

An Undergraduate Thesis

Presented to the Faculty of the School of Engineering and Applied Science

University of Virginia • Charlottesville, Virginia

In Fulfillment of the Requirements for the Degree

Bachelor of Science, School of Engineering

**Christian Hennessey Jenkins**

Spring, 2021

Department of Biomedical Engineering

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## Sociotechnical Synthesis

While my technical work and STS research are not directly related, the clinical capabilities of Microporous Annealed Particle (MAP) Gel have the potential to replace conventional fillers currently used for cosmetic surgery. Working on both of these projects concurrently has allowed me to explore the range of clinical applications of MAP Gel while also considering how various consumer bases will interact with the product. My technical research compares the cellular response of MAP Gel with three different chemical backbones in order to determine which backbone leads to the best *in vivo* and *in vitro* outcomes. My STS research explores identity formation of minority patient populations through the use of plastic surgery.

My technical research team works with the novel biomaterial MAP Gel, a microporous hydrogel that does not induce a foreign body response when implanted in vivo. The porosity and mechanical characteristics of the gel allow for natural tissue and vasculature to infiltrate the scaffold without triggering a foreign body response. Currently, MAP Gel is synthesized using a polyethylene glycol (PEG) backbone, a synthetic polymer with highly tunable mechanical properties. In an effort to ensure MAP Gel promotes an optimal cellular response, my team is comparing three chemical compositions of the scaffold: PEG, Hyaluronic Acid (HA), and Gelatin Methacrylate (GelMA). While PEG is a synthetic polymer, HA is a natural polymer found in extracellular matrix, and GelMA is naturally derived from collagen. Each of these three chemical backbones have strengths and weaknesses when it comes to, not only cellular response, but also the ease of MAP Gel integration, shelf stability, and recognizability by the immune system. The formulations were subcutaneously injected into a murine animal model to monitor the in vivo cellular response. Our clinical application is the treatment of Glottic Incompetence (GI) by using MAP Gel as a volumizing to close partitions between vocal folds that can result in speech and

respiratory issues. The same volumizing properties of MAP Gel can be used as a safer alternative to injectable fillers for cosmetic purposes.

For my STS research, I am analyzing how minority populations are interacting with plastic surgery, especially in terms of facial cosmetic procedures. There seems to be a strong western idea that plastic surgery is utilized by 'ethnic' patients to appear more 'White', despite strong rejection of this ideal by non-White users. Through my research, I highlight how minorities are subverting the claim of a singular beauty standard while reifying their own identities.

In recent years, injectable fillers have grown in popularity within the cosmetic industry, undoubtedly influencing the formation of identity. Through both my technical and STS research, I was able to delve into how a growing population may ultimately interact with the product of my research in only a few years.

I would like to thank Professor Ferguson for guiding and supporting my STS Thesis. I would also like to thank Professor Griffin, Lauren Pruett, Nick Cornell, and Kyle Limpic for their dedication and efforts that made this capstone project possible.

**Understanding varied cellular and tissue responses in Microporous Annealed Particle (MAP) hydrogels with differing chemical compositions**

A Technical Report submitted to the Department of Biomedical Engineering

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Spring, 2021.

Technical Project Team Members

Kyle Limpic

On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

Donald Griffin, Department of Biomedical Engineering

# Understanding varied cellular and tissue responses in Microporous Annealed Particle (MAP) hydrogels with differing polymer backbone chemistries

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**Abstract**

Glottic insufficiency (GI), characterized by an incomplete closure of the vocal folds, affects a large part of the geriatric patient population. Current treatments for GI include tissue fillers that rapidly degrade and often elicit an adverse immune response. Microporous Annealed Particle (MAP) gel is a novel hydrogel biomaterial that promotes natural tissue integration without triggering a foreign body response (FBR). In this approach, we perform the first comparative analysis of three different MAP scaffold (gel) formulations controlled for differences in polymer backbones. We aimed to characterize these MAP scaffolds based on several varied cellular and tissue responses. Hyaluronic acid (HA), poly(ethylene-glycol) (PEG), and gelatin methacrylate (GelMA) were used as the polymer backbones of interest due to their frequent use in MAP scaffolds in published research and distinct chemical characteristics. To isolate the effects of the chemical composition, mechanical stiffness, microsphere size, and scaffold porosity were standardized across groups. In this manuscript, we determine scaffold favorability through *in vitro* testing as well as *in vivo* analysis using a subcutaneous implant murine model.

Keywords: Glottic insufficiency, MAP scaffold, foreign body response, injectable filler

## Introduction

Glottic insufficiency (GI) is a disorder of the larynx whereby failure of glottic valve closure prevents vocal fold adduction, which is critical for functions such as phonation, respiration, and swallowing (Fig. 1) [1]. Intubation-related injury, arytenoid trauma, infection, scarring and deformation of the vocal folds, neuromuscular defects, and glottic tumor excision are among the many etiologies of glottic insufficiency[1,2]. Patients with physical damage to their glottis often have trouble swallowing (dysphagia), vocal hoarseness and difficulty speaking (dysphagia), aspiration, and recurrent pulmonary bacterial infections[1,3]. In the current standard of care, vocal cord damage can be treated by two methods: (1) injection laryngoplasty whereby tissue fillers, such as Restylane (crosslinked hyaluronic acid) or Radiesse (calcium hydroxyapatite), are introduced to augment tissue volume, or (2) surgical medialization of the larynx using non-degradable materials[4]. Both treatment options renew effective vibration during phonation and closure after swallowing[4]. However, in injection laryngoplasty, current tissue filler alternatives face many drawbacks including inflammation, infection, implant migration, and resorption after 6-12 months, which can cause severe patient discomfort and require multiple follow-up procedures[5]. Both the symptoms and treatments for glottic insufficiency interfere with patients' everyday life, prompting the need for a minimally invasive long-lasting implant solution[6].

Fibrotic scar formation and foreign body inflammation has posed challenges to traditional implant-based treatment approaches for GI[7]. Microporous Annealed Particle gels

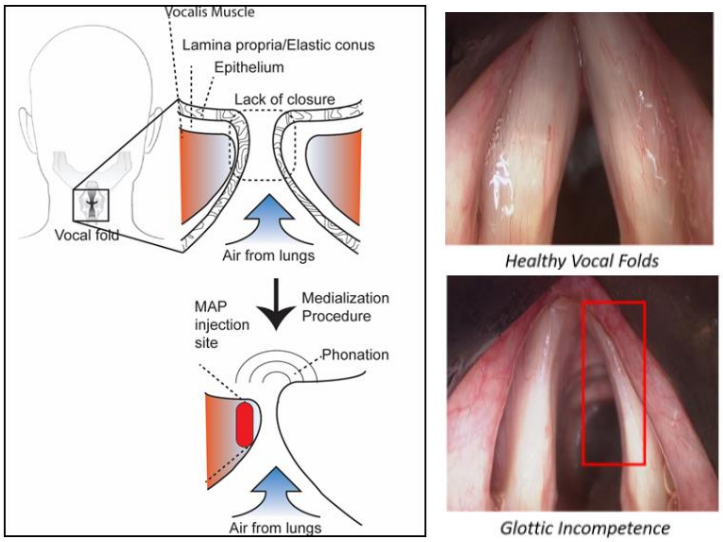


**Fig. 1. (**Adapted from Pruett et. al.) Left shows normal acoustic phonation and location of MAP implantation in injection laryngoplasty. Images at right show heathy vocal folds vs those with GI (courtesy of UVA ENT).

(MAP gels) mitigate these risks by providing a stable, microporous scaffold structure for tissue reconstruction that can be injected for minimally invasive clinical applications, without eliciting an adverse inflammatory immune response *in vivo*[8]. Key advantages of MAP in treatment of GI are the requisite mechanical stiffness profile to mimic surrounding glottic tissue conditions, tunable bioactive modifications to control cell migration and adhesion of circulating progenitor cells, porosity to mediate cellular infiltration, and scaffold resorption after laryngeal remodeling[8]. In this way, natural tissue replaces the cross-linked MAP scaffold upon degradation, resulting in volumized vocal cords and eliminating the need for chronic injection therapy.

MAP (Microporous Annealed Particle) gels are a novel class of biomaterials built via a building block assembly of individual polymer-based hydrogel microspheres that form an immobilized tissue scaffold upon secondary crosslinking (i.e. annealing) that facilitates interparticle covalent bonding[8] (Fig. 2). MAP scaffolds iterate on traditional bulk hydrogel designs where components are cross-linked in continuous volumes, an approach which is not ideal where small volumes are necessary[6,8,9]. In addition, unlike nanoporous gel constructs, MAP scaffolds do not require material degradation to promote cellular infiltration[8]. MAP scaffolds also provide a more controllable infrastructure through limitation of microsphere rearrangement and a more tunable mechanical stiffness profile when compared to traditional bulk hydrogels or other hydrogel material constructs[8,9].

It has been previously shown that biomaterial architecture is an important factor affecting the local inflammatory reaction post-implantation. Specifically, microscale porosity offers an immune-privileged response over non-porous constructs and improves wound healing *in vivo*[10]. While in recent years MAP hydrogels have established their superiority over traditional bulk nanoporous hydrogels, there still exists contention regarding the optimal polymer backbone chemistries and formulation strategies for these tissue scaffolds[11–14]. We aimed to understand whether material formulation, in particular backbone composition, is a key determinant of a regenerative tissue response.

We have selected three polymers based on their widespread application in development of biomaterial constructs, specifically MAP gel, and their varied chemical characteristics[11,13]: hyaluronic acid (HA), poly(ethylene-glycol) (PEG), and gelatin methacrylate (GelMA) (Fig. 2). HA and GelMA MAP scaffolds have been previously synthesized, but they have never been compared directly against each other or against PEG, in the context of MAP gel. HA is a natural polymer with high bioactivity and biocompatibility, often selected due to its natural occurrence within ECM[15]. PEG, however, is a bio-inert synthetic polymer that has high mechanical stability and low immunogenicity and can be crosslinked with various peptides to yield different degradability profiles. The physicochemical properties and availability of PEG make it a preferred synthetic backbone for biomaterial synthesis[13]. GelMA is derived from collagen and can mimic ECM properties to a high degree of accuracy but has low mechanical strength and thermal instability at high temperatures[16,17].

In general, natural polymers have high bioavailability and are readily accepted by the ECM due to their innate biocompatibility and high bioactivity, leading to improved protein adsorption and reduced risk of an adverse foreign body response (FBR) in porous materials[8,11,18]. Low immunogenicity paired with promotion of cellular infiltration and resorption into neutral degradation products gives natural polymers an inherent advantage over certain synthetic polymers in a myriad of biomedical applications[12]. Hyaluronic acid, or hyaluronan (HA), is a native biopolymer that has strong biocompatibility, biodegradability, tunable characteristics, and demonstrable bioactivity[12–14]. HA is highly expressed in the ECM and can be degraded by various oxidative species and hyaluronidases[15]. As the current clinical standard of care, HA hydrogel systems exist for corneal and dermal wound repair applications, such as Restylane-L. These treatment

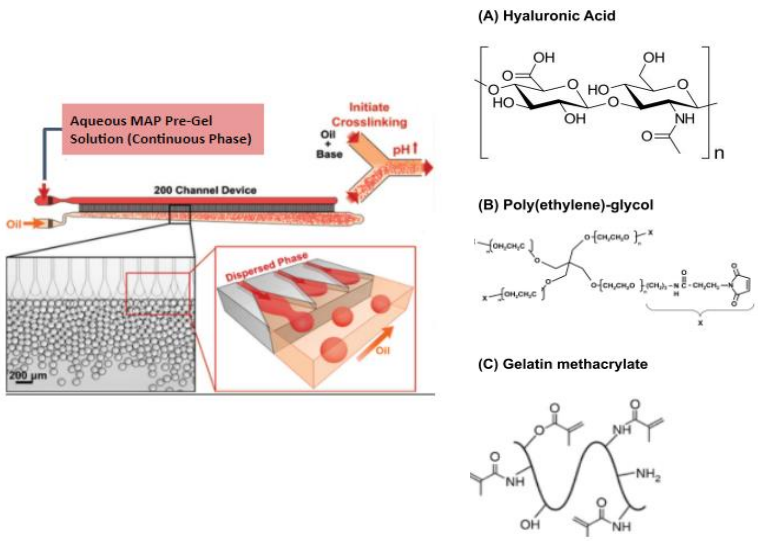


**Fig. 2.** At left is the water-in-oil droplet formation using microfluidic emulsion followed by base-catalyzed downstream covalent crosslinking of MAP microspheres. The continuous phase contains the aqueous pre-gel solution with polymer backbone, crosslinker (if applicable), RGD cell adhesive peptides, and MethMal. Picosurf surfactant and NOVEC 7500 engineered fluid were used in the oil phase to facilitate particle formation. Crosslinking was initiated by treatment with triethylamine downstream of the microfluidic device. At right are the three polymer backbone structures used in the comparative analysis. (A) HA is a natural polymer made up of repeating disaccharides. (B) PEG is a four-arm synthetic polymer. (C) GelMA consists of gelatin monomers and methacrylic anhydride linked to a polymer backbone.

pathways show great future potential for clinical translation given physicochemical tunability of HA and improvements in fabrication capabilities[15]. HA, however, depending on the source organism, can be immunogenic, and its connection with various inflammatory pathologies has yet to offer full insight into long-term clinical implications of HA treatments[15]. Gelatin methacrylate (GelMA), on the other hand, is a natural biopolymer derived from collagen hydrolysis and modified with methacrylate and methacrylamide groups to facilitate hydrogel crosslinking[16,17]. GelMA contains various cell-attaching and MMP-responsive peptide motifs, further stimulating cell proliferation and migration[17]. GelMA-based hydrogel systems exhibit strong ECM mimetic behavior, facile synthesis across different fabrication methodologies, excellent biocompatibility, and low immunogenicity[16,17]. GelMA, however, is limited by low mechanical strength, uncontrollable structural degradation, and tendency to thermally denature at normal physiological temperatures[16,19].

In contrast, synthetic polymers allow for enhanced tunability of mechanical characteristics such as elastic modulus and microsphere size, while also providing improved stability in the MAP microstructure and more controllable degradation[20]. Typically, synthetic polymers are more readily manufactured, functionalized, processed, and sterilized for implantation than natural polymers, and are more stable in response to thermal inputs. Synthetic polymer designs, however, oftentimes lack the necessary biofunctionality required for much-desired ECM mimicry, and may even elicit a strong inflammatory response *in vivo*. Poly(ethylene-glycol) (PEG) is a 4-arm synthetic, bioinert, and hydrophilic polymer, and PEG-based hydrogels have been used in numerous applications, including cell encapsulation, drug delivery, and tissue remodeling[7,21,22]. PEG polymer networks in MAP scaffolds have shown diminished foreign body response *in vivo* when compared to PEG nanoporous hydrogels[8]. PEG is also bioinert which helps to mask the implant from the host's immune system.

We attempted to make the first controlled comparison of PEG, HA, and GelMA MAP hydrogels to better understand the functional implications of altered material backbone chemistries. Following MAP scaffold characterization, synthesis, and normalization across several key physical parameters, we will use *in vitro* assays and an *in vivo* murine subcutaneous implant model to assess the varied biocompatibility and immunogenicity profiles for each of these MAP formulations.

## Results

### *MAP Scaffold Mechanical Characterization and Matching*

The Young's moduli of GelMA, HA, and PEG MAP scaffolds were matched to within one standard deviation of the mechanical stiffness of soft tissues, at 18 kPa (Fig. 3)[23]. Microsphere diameters for each condition were standardized to within one standard deviation of 65 µm to control for microsphere size. Similarly, MAP conditions were controlled for differences in matrix porosity since microsphere diameter has been previously shown to correlate with pore diameters[8]. Based on microsphere sizes and previous pore analysis, the pore diameters are expected to be approximately 15 µm[8]. Polydispersity indices (PDIs) were calculated, and all were below 1.05, indicating uniform particle populations.

### *In vitro Viability and Migration Assays*

An *in vitro* viability assay was used to evaluate how each MAP scaffold condition was tolerated by human dermal fibroblasts (HDFs) suspended in the annealed MAP scaffolds after 24 hours. Control conditions were HDFs cultured in fibroblast-specific media on TC plates. As determined by a one-way ANOVA and post-hoc multiple

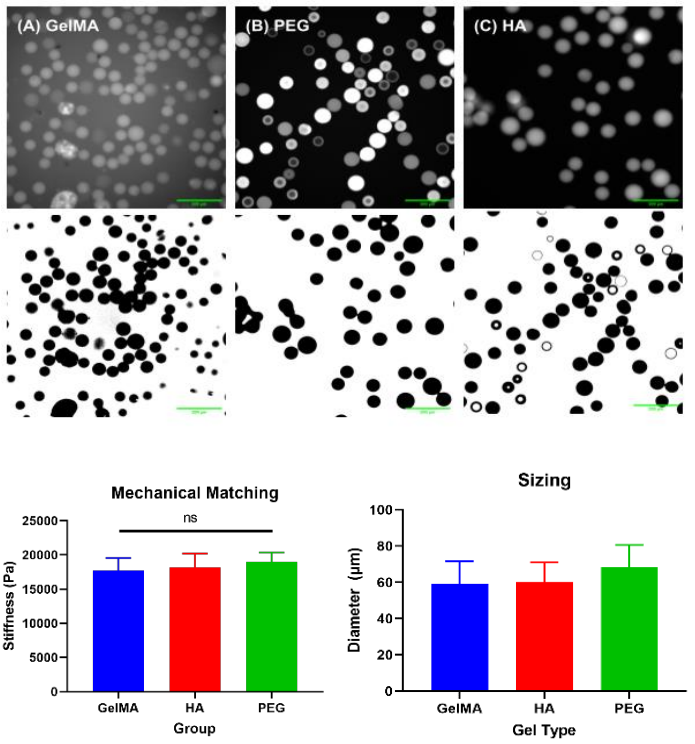


**Fig. 3. Standardization of scaffold physical parameters.** At top, GelMA, PEG, and HS hydrogel microsphere images under TL confocal microscopy (top: raw, bottom: threshold). Scale bars = 200 µm. At bottom left, Young's modulus was matched to that of vocal fold tissue (18kPa) across all GelMA MAP, HA MAP, and PEG MAP. At bottom right, microsphere sizing was standardized to 60 µm using oil-in-water microfluidic emulsion.

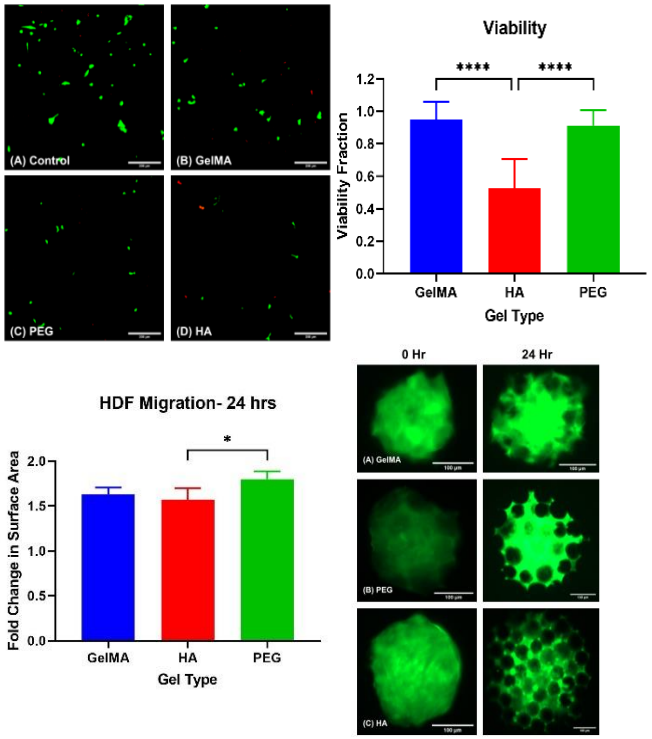


**Fig. 4. *In vitro* viability and migration assays and *in vivo* H&E.** At to left, live cells (GREEN) and dead cells (RED) are shown for the control and treatment groups. Scale bars = 200 µm. At top right, viability fraction of HDFs within the HA MAP scaffold was significantly lower than the GelMA MAP and PEG MAP formulations. At bottom, left fold change in cell surface area over 24 hours revealed higher cell migration into the PEG MAP scaffold compared to other groups. At bottom right are images of CellTracker-stained

comparisons tests (Tukey's HSD), GelMA and PEG MAP conditions were found to have significantly greater viabilities compared to the HA MAP formulation ($p<0.0001$), with live cell percentages of 94.87% and 91.34%, respectively. GelMA and PEG viability percentages were not significantly different from one another ($p=0.6799$) (Fig. 4). HA MAP condition elicited markedly poor HDF viability of 52.71%, most likely due to contaminants or endotoxins present in the stock sourced from the supplier. However, *in vivo* studies are necessary to confirm this hypothesis**.**

An in vitro migration assay was used to assess how well HDF spheroids were able to migrate throughout the MAP scaffolds. PEG MAP was found to have an area coverage fold change significantly greater than HA MAP ($p<0.0001$), but not GelMA MAP ($p=0.09$), according to a one-way ANOVA and Tukey's HSD multiple comparisons test. Cell migration within GelMA MAP was not significantly different from HA MAP ($p=0.70$) (Fig. 4). PEG MAP was the most effective at facilitating cellular migration, with an area fold change of 1.80, while HA and GelMA MAP were slightly less effective, with fold changes of 1.57 and 1.63.

### *Murine in vivo Subcutaneous Implant Study*

Histologic evaluation of immunogenicity of subcutaneous MAP implants in vivo

Twelve 8-week-old Swiss-Webster mice received dorsal subcutaneous injections of each MAP scaffold and implant-tissue samples were harvested and fixed at either 1 week or 1 month (N=6) (Fig. 5). Notably, we were not able to distinguish between the MAP implants in mouse 1 (1 week) or mouse 7 (1 month) at the time of harvest. A sample size of N=5 mice were used for each timepoint.

To evaluate the foreign body response (FBR) to MAP implants across formulations, we employed H&E staining to quantify the width of the inflammatory capsule around the MAP scaffolds, at both 1 week and 1-month intervals. At 1 week, GelMA (27.60 µm) and PEG (21.06 µm) did not show significantly different encapsulation layer thicknesses ($p=0.6387$), while HA elicited an FBR with significantly higher encapsulation (96.43 µm) when compared to GelMA and PEG ($p<0.0001$), respectively (Fig. 6). At 1 month, encapsulation of the GelMA MAP scaffold (30.85 µm) was

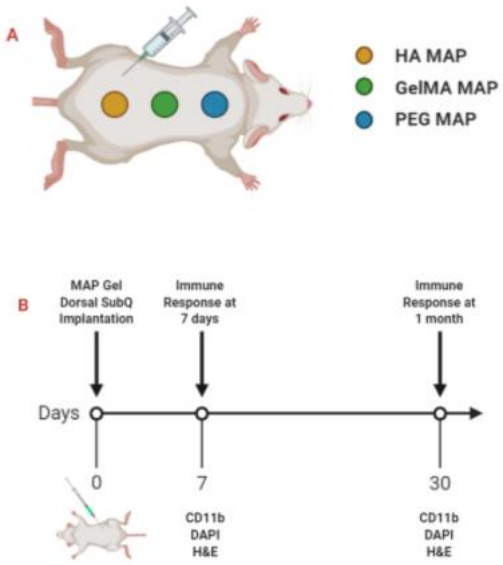


**Fig. 5. Schematic of murine animal model.** (A) Schematic of subcutaneous injections in murine model and (B) timeline of injection and scaffold harvest timepoints with appropriate stains.

not significantly different from either PEG (13.21 µm) (p=0.6457) or HA MAP (65.60 µm) (p=0.1844) formulations. However, HA and PEG MAP conditions were found to have statistically significant differences in scaffold encapsulation thickness. These results were determined using a one-way ANOVA followed by Tukey's HSD multiple comparisons test across MAP scaffold treatment groups.

Using CD11b immunofluorescence staining we were then able to quantify the general cell-based immunological response to the injected MAP scaffolds. CD11b is a general marker for cells of the myeloid lineage and measurement of DAPI-CD11b cell colocalization provides for assessment of the general inflammatory reaction elicited by each MAP condition (Fig. 7). At 1 week, GelMA and PEG MAP scaffolds had a DAPI-CD11b+ colocalization percentages of 26.82% and 48.36%, respectively. However, GelMA and PEG MAP conditions did not show significantly different levels of DAPI-CD11b+ colocalization at 1-week (p=0.1035). At 1 month, PEG MAP had a CD11b+ cell fraction of 37.66% while GelMA MAP showed a higher percentage of 59.67%. However, CD11b+ presence in GelMA and PEG MAP at 1 month were not significantly different (p=0.0752). P-values for DAPI-CD11b+ colocalization fractions for both timepoints were determined by a paired, two-tailed student's T-test (N=5). It should be noted that a GelMA implant from mouse 8 showed a particularly prominent inflammatory response,

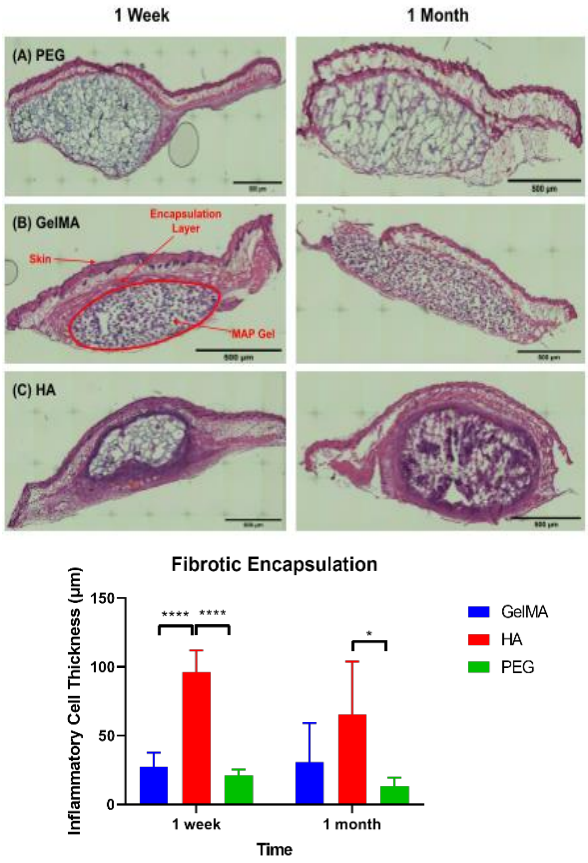


**Fig. 6. H&E histology images and fibrotic encapsulation analysis.** (A) PEG MAP shows scaffold infiltration with low fibrotic encapsulation. (B) GelMA MAP scaffold shows healthy morphology and low fibrotic encapsulation. (C) HA MAP with large fibrotic encapsulation and cell lysate stained pink within the scaffold. HA MAP had significantly more fibrosis at 1 week and 1 month time points.

with a DAPI-CD11b+ colocalization of 84.10%. Surprisingly, GelMA MAP implants demonstrated an increase in DAPI-CD11b+ colocalization from 1 week to 1 month, while PEG MAP showed a decrease from the 1 week to 1-month timepoints. HA MAP implants were not analyzed for CD11b due to suspected contamination discovered during viability assay and H&E histological analysis.

## Evaluation of cellular infiltration facilitated by MAP implants in vivo

To quantify the level of cellular infiltration into the MAP implant, cell nuclei were stained with DAPI (N=5). Our endpoint metric was the number of cell nuclei per scaffold area ($mm^2$). At 1-week post-implantation, GelMA (1098 cells/ $mm^2$) was found to have significantly higher levels of cell infiltration when compared to PEG (297 cells/$mm^2$) (p=0.0082) (Fig. 7). At 1-month post-implantation,

however, GelMA (1034 cells/ mm$^2$) and PEG (785 cells/ mm$^2$) promoted comparable cell infiltration from surrounding bulk tissue (p=0.5755). Hypothesis testing on raw cell infiltration data was performed using a paired, two-tailed student's T-test. HA MAP implants were not analyzed for cellular infiltration due to the exacerbated immune response noted previously.

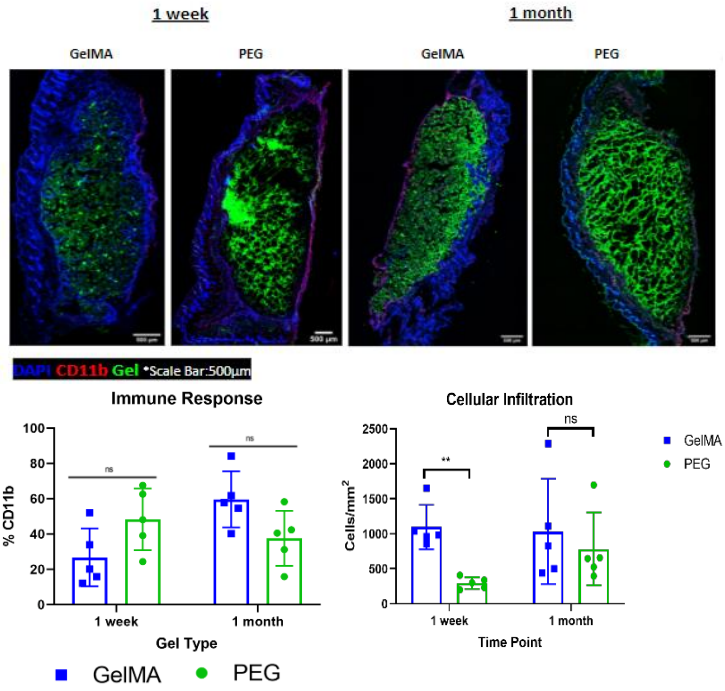


**Fig. 7. CD11b+ and DAPI stained tissue section images and analysis.** At top is shown CD11b+ cells (RED), cell nuclei (BLUE) and MAP scaffolds (GREEN) for GelMA and PEG MAP implant-tissue sections. At bottom left CD11b - DAPI colocalization percentages were not significantly different between the GelMA and PEG MAP conditions at either time point. At bottom right, cellular infiltration into PEG MAP increased from the 1 week to the 1-month time point.

## Discussion

To effectively treat glottic incompetence in vocal fold paralysis or presbyphonia, biomaterials need to have minimal immunogenicity, biocompatibility, injectability, tunable elastic moduli, and customizable degradation kinetics. The novel MAP platform has been shown to offer these important characteristics, but the functional implications of altering backbone chemistries within MAP scaffolds are still yet unknown. We have attempted to profile three separate material formulations based on measurement of immunogenic and biocompatibility endpoints, using MAP scaffolds as a biomaterial system.

### *Material Mechanical Characterization and Matching*

Varying the HA concentration and PEG and GelMA MAP scaffold weight percentages allowed us to finely tune the mechanical stiffness for each condition. Instron compression testing was used to measure the mechanical stiffness of MAP scaffold formulations to both standardize elastic moduli across treatment groups and match the stiffness of soft tissues, at approximately 18 kPa. We then quantified microsphere sizes using confocal microscopy and image analysis. From our initial results we noticed that GelMA did not swell as much as we had expected, so we elected to use the 55-65 μm channel microfluidics device for synthesis of the GelMA MAP scaffold. For HA and PEG MAP scaffolds, we used the 45-55 μm channel devices. Otherwise, we did not alter relative flow rates between the continuous and oil phases to further control microsphere size. We thus achieved our desired outcome of microsphere diameters within one standard deviation of 65 μm.

### *Assessment of Tolerability and Biocompatibility of MAP Scaffold Formulations*

Analysis of cell viability within the MAP scaffold microenvironment indicated that the HA formulation was likely contaminated. GelMA and PEG performed as expected in maintaining HDF viability percentages at above 90% when compared to control conditions. HDF migration assay analysis suggested that PEG MAP scaffolds were most effective at permitting cellular migration *in vitro*, but migration within the GelMA MAP scaffolds was not significantly lower than PEG. This is evidence that PEG has comparable tolerability and biocompatibility to GelMA *in vitro*. Surprisingly, HA MAP and GelMA MAP scaffolds did not exhibit significantly different cell migration, as there was between HA and PEG. We attribute the high rate of spheroid migration in the HA condition to both imaging only after a short time span (24 hours) and spheroid-protection of HDFs.

Cell nuclei were then stained with DAPI to quantify cellular infiltration. While we observed a significantly higher level of cell infiltration in the GelMA MAP scaffold at 1 week, GelMA and PEG performed at comparable levels at the 1-month timepoint. This is most likely due to the presence of cell adhesive motifs in GelMA. Our preliminary results suggest that manipulating material backbone composition does not significantly affect cell infiltration at 1 month.

### *Assessment of Local Immunogenicity elicited by MAP Scaffold Formulations*

Quantification of fibrotic encapsulation suggests that HA MAP scaffold samples were contaminated. A foreign body response (FBR) may be measured by the thickness of the fibroblast layer formed around an implant, so the significant

increase in fibrotic encapsulation thickness around HA gel samples indicates that a severe foreign body response was triggered. Furthermore, the H&E histology stains showed porous networks of cells within GelMA and PEG MAP formulations, while HA MAP scaffolds contained densely packed immune cells.

CD11b-DAPI colocalization was then analyzed to quantify the presence of myeloid lineage cells and macrophage activity across treatment groups. We observed markedly high levels of CD11b+ cell density within the MAP scaffolds and a surprising increase in myeloid cell recruitment within the GelMA MAP implant from 1 week to 1-month timepoints.

Mouse 8 (1 month) showed a very high DAPI-CD11b+ colocalization for GelMA, which is indicative of a strong inflammatory response. This has likely skewed the cell infiltration results upwards and led to large standard deviations in our cell infiltration data. Having performed an outlier analysis (Grubb's Test), however, it was determined that though the CD11b+ cell presence in mouse 8 (84.10%) was the most extreme measurement at 1 month, it was not a significant outlier ($p>0.05$). For PEG, low immunogenicity has been previously shown for a similar PEG MAP formulation in a subcutaneous murine model, as well as in dermal and neural tissue repair[6]. We hypothesize that both the PEG and GelMA MAP implants experienced an elevated local inflammatory response induced by the adjacent toxic HA MAP implants. While CD11b+ cell presence in GelMA and PEG was slightly higher than expected at 1 month, neither MAP implant condition elicited an adverse immune reaction, as confirmed in the H&E staining. In general, is appears that PEG MAP scaffolds elicited a slightly more immune-privileged response when observing a smaller fibrosis at 1 week and 1 month, and lower CD11b+ cell density at 1 month *in vivo*. Overall, however, there is little conclusive evidence that variation in implant immunogenicity is dependent upon manipulation of material backbone chemistry, when comparing GelMA and PEG MAP conditions at 1 week and 1 month.

### *Concluding Remarks*

Both GelMA, a natural polymer backbone, and PEG, a synthetic polymer backbone, when synthesized as MAP scaffolds, yielded favorable results with minimal immune response. In terms of fibrotic encapsulation, GelMA MAP and PEG MAP both had similarly low levels of fibrosis at 1 week, with PEG appearing to further decrease at the 1-month time point as GelMA increased. The immune response, measured by CD11b, resulted in a lower immune response for GelMA than PEG at 1 week, which may indicate that natural polymer backbones are more easily able to avoid an initial FBR. At 1 month, however, GelMA had a slightly higher FBR than PEG, indicating that synthetic polymers may be better for long term applications. Similar trends were observed in cellular infiltration analysis, where GelMA had significantly more cellular infiltration at 1 week but held a statistically insignificant margin to PEG at 1 month. Synthetic polymers also have strengths over natural polymers in terms of physicochemical tunability and customizable degradation kinetics which may prove to be more favorable for clinical use in treatment of GI. Due to source contamination of HA, no conclusive results were obtained from CD11b immunofluorescence or cellular infiltration analysis. Further research is necessary to evaluate the efficacy of an HA MAP formulation. Future studies of M1 and M2 macrophage polarization with CD68+ co-staining would be useful to better evaluate the inflammatory response of various material compositions. We could also stain for smooth muscle actin and different collagen types to further characterize the fibrosis. A 12-week degradation study would provide insight into the stability of each gel *in vivo*, a key feature of volumizing fillers. Overall, while our results suggest that material selection is not the primary determinant of immunogenicity and cellular infiltration, PEG-based MAP hydrogels appear to offer more advantageous *in vivo* responses. This serves to corroborate previous studies which have determined that PEG-MAP gels are a suitable material choice for vocal fold augmentation in glottic incompetence.

## Materials and Methods

### *Biomaterial Formulation, Synthesis, and Characterization*

Input material and sources

Thiolated hyaluronic acid (HA-SH) was purchased from Creative PEGworks (Chapel Hill, NC). Four-arm poly(ethylene-glycol) maleimide (PEG-MAL, 10kDa) was purchased from Nippon Oil Foundry, Inc. (NOF Corporation, Kawasaki, Kanagawa, Japan). Matrix metallo-protease (MMP) degradable crosslinker (MMP) (Ac-GCGPQGIAGQDGCG-NH2) and arginylglycylaspartic acid cell adhesion peptide (RGD) were purchased from WatsonBio Sciences (Houston, TX). Type A porcine skin gelatin and methacrylic anhydride were purchased from Sigma-Aldrich (Millipore Sigma). All input materials were dissolved in ultrapure MilliQ water or 0.1% trifluoroacetic

acid (TFA) and aliquoted appropriately. Aliquots were then lyophilized and stored at -20 deg. C.

MAP scaffold formulations

The HA-SH MAP formulation was composed of HA-SH backbone dissolved in ultrapure MillQ water at 10 mg/mL and PEG-Mal crosslinker, RGD cell adhesion peptide, and MethMal solution dissolved in 3.7 pH 10x Dulbecco's phosphate-buffered saline (DPBS). The 3.2 wt% PEG MAP formulation consisted of a 4-arm PEG-Mal backbone, an RGD cell adhesion peptide, and MethMal solution (to immobilize the microsphere network) dissolved in 3.8 pH 10x DPBS and MMP-degradable crosslinker dissolved in pH 7.4 1x DPBS. HA and PEG MAP formulation solutions were mixed in equal volumes to form aqueous pre-gel solution. Type A porcine skin gelatin underwent methacryloyl functionalization using a previously published method[24]. Due to the presence of native RGD sequences and methacrylate-methacrylamide bridging crosslinks, 8 wt% GelMA MAP formulation consisted solely of gelatin methacryloyl (gelatin-methacrylic anhydride, GelMA) microspheres.

Macro-scale gel synthesis

Macro-scale gels did not undergo microfluidic emulsion but were formed using the same formulation as the microgel solution. The macro scaffolds were formed by placing the 150 µL sample between two glass slides, 2 mm apart. Rheology was used to monitor gelation time, according to the rheometer's gelation curve. After gelation, the scaffolds swelled in 1x DPBS overnight at 37 deg. C. Mass was recorded before and after swelling to determine an equilibration ratio.

Mechanical stiffness matching

Following swelling in 1% DPBS, macro gels were wicked of excess moisture and subjected to Instron compression testing to determine elastic (Young's) modulus. Backbone polymer weight percent was varied to achieve mechanical stiffness similar to that of soft-tissue elastic moduli, within one standard deviation of 18kPa.

MAP scaffold production, purification, and sterilization

To fabricate the MAP scaffolds, we use a stepwise, two-phase, water-in-oil emulsification process to produce a stable and monodisperse population of ~65 µm microspheres. Selection of appropriate micro fluidic device channel heights and regulation of relative flow rates between the aqueous and oil phases was informed by equilibration ratios. PEG and HA MAP scaffolds were fabricated using a PDMS mold for 45-55 µm microspheres while GelMA MAP scaffolds were produced using a PDMS mold for 55-65 µm microspheres. Picosurf surfactant (Sphere Microfluidics) was diluted to 1% using NOVEC 7500 (3M). Using a syringe pump the oil-surfactant and aqueous pre-gel phases were run through the microfluidic device at a rate of 5 mL/hour. MAP microspheres were crosslinked downstream of droplet formation via Michael-type addition. Gelation was catalyzed in the HA and PEG formulations via pH modulation with triethylamine (Sigma Aldrich) at a concentration of 20 µL/mL of gel. As a result of the inherent thermal instability of GelMA microspheres at temperatures above 4 deg. C, we used a previously published approach to partially photocrosslink GelMA microbeads in the oil phase. GelMA microspheres were exposed to 365 nm UV light for 60s at an intensity of ~100 mW/cm$^2$ in parallel with emulsification of the aqueous phase in the microfluidic device. MAP scaffolds were then washed 3x with NOVEC 7500 engineered fluid at 1x gel volume. Next, MAP scaffolds were swelled in 1x DPBS at 5x gel volume and washed subsequently three times in NOVEC 7500 engineered fluid (1x gel volume). Then the NOVEC 7500 oil was removed, and MAP scaffolds were washed again with 1x DPBS (5x gel volume) and Hexanes (5x gel volume), followed by ultracentrifugation at 4696g for 5 minutes. In a biosafety hood, MAP scaffolds were washed 3x with 70% IPA (5x gel volume) and again centrifuged at 4696g for 5 minutes. MAP scaffolds were then stored at 4 deg. C in 70% IPA until use[25].

Microsphere size characterization

MAP scaffolds were first conjugated with an Alexa Fluor 488 (ThermoFisher) during microsphere formation. These samples were diluted 1:1000 in 1X DPBS for visualization in a 96-well plate (Costar) and imaged using an ImageXpress confocal microscope in the FITC channel (Molecular Devices). We used the 'Analyze Particles' function in ImageJ to filter for microspheres according to circularity (0.7-1.0) and minimum size (<680 µm$^2$), and then determined average microsphere diameter and polydispersity indices (PDI) for each MAP condition. PDI is equivalent to $D_W/D_N$, where the weighted average ($D_W$) was calculated by $D_W = \sum N_i D_i 2/\sum N_i D_i$ and number average ($D_N$) was calculated by $D_N = \sum N_i D_i/\sum N_i$[6]. A minimum of 150 microspheres were analyzed for each condition.

***In vitro Assays***

Viability assay

Using a previously published method for quantification of cell viability[26], we first took dried, sterilized, and purified MAP scaffolds and mixed 1:1 with a 0.2 mM lithium phenyl-2,4,6-trimethylbenzoylphosphinate (LAP) photoinitiator solution (Sigma), followed by a 15 min incubation at room temperature and re-drying by centrifugation at 25,000g. We then suspended 80% confluency HDF cells in the prepared MAP scaffolds at a seeding density of 1000 cells/ µL. 15 µL of the cell-laden MAP scaffolds (N=4) per condition were pipetted into a 48-well plate (Falcon) and then underwent light-based annealing using 365 nm UV light at an irradiance of 8.35 mW/cm$^2$ for 30 s (ThorLabs PM100D) 15.6 cm above the gel. HDFs in MAP gels were the cultured in HDF-specific growth media and incubated for 24 hours. After 1x DPBS washing at 24 hours, we then used a LIVE/DEAD staining

kit with a two-color discrimination system (ThermoFisher) and samples were imaged using the FITC and Texas Red filters of an ImageXpress Micro Confocal. Briefly, a 50 μm z-stack with 5 μm steps was centered at the midpoint of the scaffold and assembled into a Maximum Intensity Projection (MIP) of live and dead cells. Using a custom Fiji cell enumeration pipeline with a minimum size threshold of 100 pixels (68 $\mu m^2$) to output live and dead cell counts for each condition, which were then converted to fold change over control[27].

Migration assay

We used a previously published method for characterizing and quantifying cell migration within the 3D MAP scaffold environment *in vitro*[27]. Prior to the start of the study, HDFs were fluorescently tagged using AF488 CellTracker (Fisher). We prepared 20 μL spheroids of these HDF cells at a concentration of 50,000 cells/mL supplemented with 5% methylcellulose using the hanging droplet method of formation in a petri dish (Falcon) containing 5 mL of sterile 1x DPBS. Following an overnight incubation in cell culture media, MAP scaffolds were suspended 1:1 in 0.2 mM LAP photoinitiator solution (Sigma). 40 μl MAP scaffold samples (N=4 per condition) were annealed using 365 nm UV light at 14.8 $mW/cm^2$ for 30s in a 48 well plate. Spheroids were incubated for 24 hours at 37 deg. C and then pipetted onto the annealed scaffolds at the bottom of the 48-well plate. 10X images were acquired in the FITC channel at 0 and 24 hours to evaluate cell migration in each MAP condition (EVOS). Images were analyzed with Fiji using a previously described method by thresholding to calculate fold change in spheroid area within the porous scaffolds over 24 hrs.

Statistical methods

All statistical analysis was performed using GraphPad Prism software. ANOVA followed by multiple comparisons post-hoc tests (Tukey HSD) was used to compare all *in vitro* assays and the fibrotic encapsulation data. A student's t-test was used to assess statistical differences in cellular infiltration and CD11b presence in subcutaneous implants. We used a Grubb's Test to perform an outlier analysis on CD11b+ 1 month data for GelMA. All data is presented as mean+/- standard deviation.

***Murine Subcutaneous in vivo Study***

MAP scaffold preparation

MAP scaffolds were first washed 5 times with sterile DPBS and then suspended in a 40 μM solution of Eosin-Y (Acros Organics, Thermo Fisher Scientific) to allow for light-based photo-annealing. MAP scaffolds were then centrifuged for 5 minutes at 4696g and wicked of excess moisture, then loaded into BD 1 mL syringes using a 100 μL positive displacement pipette (Gilson MicroMan).

MAP scaffold subcutaneous implantation, harvesting, and fixation

100 μL of each MAP scaffold was implanted via injection using a BD 1 mL syringe into three respective dorsal subcutaneous sites on 8-week-old Swiss-Webster mice, N=6 for 7 day and 1 month time points, respectively. Injection locations were rotated for each mouse. Each implant was annealed using white light emitting diode (LED) light (Thorlabs DC200, Thorlabs, Newton, NJ) for 1 minute (1000 mA, 15cm away). Prior to implant harvesting, mice were humanely euthanized using an overdose of isoflurane followed by cervical dislocation. Implants were excised using surgical scissors and immediately placed in OCT compounds in embedding blocks on dry ice and transferred to the -80 degree C freezer for storage until sectioning.

Slide preparation

Subcutaneous tissue-implant samples were equilibrated to -20 deg. C, and then were sectioned into 20 μm thick layers using a cryostat (Cryostar NX50; ThermoFisher Scientific) and placed on slides. Tissue sections were stored at -80 deg C until staining.

Histological and immunofluorescence analysis

Hematoxylin and eosin (H&E) staining was performed using a previously developed protocol for frozen tissue samples[6]. Tissue sections from 1 week and 1 month time points were first fixed with cold acetone for 10 minutes. Next, samples were rehydrated with DPBS and then blocked with 5% bovine serum albumin, 5% milk, 5% fetal bovine serum for 30 minutes at room temperature. To quantify myeloid cell penetration into the MAP scaffolds, CD11b primary antibody (Invitrogen MAB-16527, 1:100 dilution; Invitrogen, Carlsbad, CA) was applied and tissue sections were incubated at 4 deg. C overnight. Sections were then washed with 1x DPBS and secondary fluorescent antibody (Alexa Fluor 647 goat anti-rat, Invitrogen A-11081, 1:1000 dilution; Invitrogen) was applied for 1 hour at room temperature. Slides were once again washed with 1x DPBS and mounted with a Prolong Anti-Fade with 4′,6-diamidino-2-phenylindole (DAPI) mounting media (ThermoFisher Scientific) to label cell nuclei. Imaging was performed using an ImageXpress Micro Confocal High Content Analysis Imaging System (Molecular Devices). Image data was processed, filtered, and analyzed using a customized Fiji and MATLAB pipeline to output the number of nuclei per scaffold area and CD11b-DAPI colocalization percentage[25].

Statistical methods

For the H&E staining to assess fibrosis between HA, PEG, and GelMA MAP implants, statistical analysis was performed using GraphPad Prism software (San Diego, CA). We first used a one-way ANOVA to compare the

means of each treatment group. This was followed by a multiple comparisons test (Tukey's HSD) to determine if there were significant differences between individual pairs of treatment groups. For the CD11b staining of myeloid cells in PEG and GelMA MAP implants, we used an unpaired, two-tailed student's T-test to determine if CD11b+ cell density was significantly different between these two groups.

## End Matter

### *Author Contributions and Notes*

C.J., K.L., L.P., and N.C. designed experiments. LP, NC, and JT performed in-lab experiments. CJ, KL, and LP performed data analysis. And CJ and KL wrote manuscript. LP, NC, and DG edited manuscript.

D.R.G. is the chief scientific officer for and owns shares of Tempo Thera, Inc. This article includes similar technology, but no relationship in any form exists with the company, including intellectual property.
Otherwise, the authors declare no conflicts of interest.

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**Analysis of how self-image is generated through the use of cosmetic surgery**

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**Christian Hennessey Jenkins**

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On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

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## Analysis of how self-image is generated through the use of cosmetic surgery

The destigmatization of plastic surgery mixed with stable economic growth over the past decade has led to an increase in the number of racial minority patients in America seeking cosmetic surgery (Wimalawansa et al., 2009). This diversifying patient population is redefining what it means to achieve beauty through plastic surgery. Within the field of plastics, there are medically defined proportions that dictate the structure and appearance of an ideal physique, especially when considering facial procedures. Historically, the consumer base of plastic surgery in America has been wealthy White women, so many medical proportions are, subsequently, based on this single model. As technology advanced, cosmetic changes became subtler, but the basis of these standards is still largely unchanged. In recent decades, as physicians have begun treating an increasing number of non-White patients, the need for a more individualized approach has become apparent. The plastic surgery term for a select range of mostly facial cosmetic procedures on non-White patients is known widely as 'ethnic plastic surgery' and non-White patients as 'ethnic patients' (Menon, 2017). Ethnic patient proportions were borne out of patient demand to receive care that coincided with their racial and ethnic identity, instead of an identical feature that was applied to many White patients. While the need to preserve a patient's identity is widely accepted within the medical field, the standards that surround treating non-White patients has become a hot topic of discussion. Outside of plastic surgery, there is a prevalent perception that non-White people use plastic surgery to look White, which is an assumption that oversimplifies beauty into a monolith and disregards the motivations of non-White patients altogether. Non-White plastic surgery patients strongly reject this assertion, as in the case of the unique aesthetics associated with the plastic surgery hub of Seoul, South Korean. In an effort to address the increasing number of ethnic procedures, medical experts have published rhinoplasty classifications to guide treatment and increase satisfaction rates, but ethnicity-based classes may have the opposite effect. Pursuing treatment based on social constructs, instead of structural features, may enforce existing stereotypes and hinder more effective treatment (Menon, 2017). This research will explore how minority patients interact with plastic surgery in order to generate an ideal self-image, and the role that ethnicity plays.

## The Rise of Cosmetic Procedures

The origins of plastic surgery were borne out of a need to treat severely disfigured soldiers who were injured during World War I (*History of ASPS*, n.d.). Over the following decades, plastic surgery was formally integrated into medical schools and public hospitals to treat a range of injuries, mostly facial lacerations and burns. In the 1980s, President Clinton mandated that reconstructive breast augmentations be covered by health insurance following a mastectomy. Despite the rapid professional success and technological advances within the field of plastics, the public view in the 1990s was that of plastic surgery-induced disfigurement. Marred by oversaturated images of celebrities with botched surgeries, a study by ASPS found that most Americans at the time did not know that plastic surgery included reconstructive surgery (*The 1990s | History of ASPS*, n.d.). Additionally, as health insurance companies began to offer smaller reimbursements for reconstructive surgeries, surgeons turned to the more attractive liquidity of cosmetic procedures, citing an inability to be profitable in the field of reconstruction. As insurance companies backed away, plastic surgeons turned to those who could afford the unsubsidized cost of elective cosmetic procedures, wealthy White women. In 2005, 88% of cosmetic surgery patients were women and in 2004, 84% were White with an average cost of $3235 among the five most popular procedures (*2005 Plastic Surgery Statistics*, 2005). This gender and racial distribution likely contributed to the prevalent association between plastic surgery and the perceived desire to have stereotypically White facial features.

## Korea Rejects White Beauty Standards

Seoul, South Korea holds the top ranking for most cosmetic surgeries per capita, with more than 20% of women undergoing a cosmetic procedure, compared to only 5% of women in the United States (Kurek, 2015.). Unlike the United States, however, the highly commercialized market of cosmetic surgery has completely normalized the industry. South Korean patients often associate plastic surgery with professional and social goals, opting for procedures that enhance highly sought-after facial characteristics like double-eyelid surgery, jaw-shaping surgery, and rhinoplasty. These procedures, however, are also the

subject of intense scrutiny in the discussion of whether plastic surgery is being used as a tool to appear White, a practice termed “deracializing”.

While South Koreans rarely, if ever, cite a desire to look more White as a contributing factor for plastic surgery, critics often cite the controversial history of cosmetic surgery in South Korea as evidence of deracialization. The double eyelid surgery, where sutures are used to convert a monolid into a double eyelid, was made popular during the Korean War by the plastic surgeon David Millard (Kurek, 2015). Millard’s work was based on deeply anti-Asian stereotypes and many suggest that this introduced a sense of inferiority among Koreans to White beauty standards. This western influence was further complicated by the introduction of mixed-race children left behind by GIs. Proponents of facial cosmetic surgery in South Korea push against claims of western influence on beauty, instead citing both historical and modern Asian beauty standards.

Historians often point to the fact that the attractiveness of double eyelids has existed since ancient China due to the rarity of the feature, and that double eyelid surgery was performed as early as 1895 in Japan (Chow, 2014). Much of this evidence predates western influence on Asian culture, suggesting that Korean beauty standards exist in absence of their western White counterparts. Scholars also warn that double eyelids should not be associated with Whiteness, considering about 50 percent of East Asians currently carry this feature. Furthermore, surgeons in Korea highlight the major differences that exist between the ideal facial characteristics of Korean and American patients. Korean patients often opt for V-line jaw surgery to create a small pointed chin and soft cheekbone projection, which contrasts the American ideal of prominent cheekbones, square-jaw, and square-chin. In terms of double eyelid surgery, patients reference motivations associated with appearing less tired and more defined, and increasingly credit the attractiveness of Korean pop (K-Pop) megastars and other cultural media influence to the beauty of large eyes (Stone, 2013). Korean and American surgeons, alike, rail against the notion that Asian patients are seeking White features, often predicting the malpractice lawsuits that would follow such a procedure.

Plastic surgery is seen by patients as a tool to achieve the ideal-self within the bounds of modern cultural beauty, strongly rejecting any singular beauty standard across demographics.

The differences in beauty perceptions between American and South Korean cultures were further studied by Bissell and Chung. 17 images of models' faces were presented to American and South Korean undergraduate students, and the attractiveness and femininity of the models were rated. Results indicated "there were significant differences on AttE [attractiveness evaluations] between US and South Korean participants" as well as "their projections on how society would view the model in attractiveness" (Bissell & Chung, 2009). These findings support the theory that beauty is based on culturally-specific indicators, and supports the idea South Korean patients are not striving to look White, considering perceived attractiveness between cultures is not constant. While this study only examines South Korea and the United States, the similar claims of beauty by American ethnic minorities indicates that ethnic subcultures within the United States most likely subscribe to beauty standards based on their own unique culture.

The notion that ethnic patients use plastic surgery to appear more White establishes an unfair standard in which only White patients can utilize cosmetic surgery free of underlying assumptions of self-hate. Elfving-Hwand and Park analyzed how Australian television covers the topic of Asian deracialization through cosmetic surgery, concluding that Australian media imposes an uncomfortable choice in which "Asian-Australian subjects are allowed only two positions, namely, the 'authentic' (unmodified) body and the body that seeks to conform through undergoing surgery" (Elfving-Hwang & Park, 2016). The proposal of these two impossible choices may explain why the view of plastic surgery as a tool for oppression is still relatively prevalent in western society. Of the choices previously presented, the only explanation for ethnic plastic surgery is conformity to a White norm. This explanation may indeed be a vehicle for oppression, except that it has been generated out of a fundamental mischaracterization of ethnic patients' motives and an unwillingness to believe ethnic patients in their claims against deracialization. The continued portrayal of ethnic patients rejecting their ethnicity is significant because it may serve as a barrier for ethnic patients

considering plastic surgery. Phrasing discussions about deracialization around 'protecting' ethnic patients disregards their explicit motivations and undermines accessibility to treatment.

## Defining Rhinoplasty as 'Ethnic' is Counterproductive

If both surgeons and patients reject the notion of 'caucasionization' in favor of individuality, then is there merit to defining specific classifications of cosmetic procedures based on ethnicity? In other words, is it reasonable and useful to govern a rhinoplasty by the ethnicity associated with the patient? And if surgeons are careful to preserve ethnicity through surgery, then is ethnicity malleable and mutable? In Menon's analysis of ethnic rhinoplasty terminology, she explains how they "draw upon existing cultural stereotypes as well as physical variation" (Menon, 2017). Ethic plastic surgery is the umbrella term ascribed to procedures on ethnic patients, often with regard to a facial feature commonly associated with the patient's ethnicity. The ethnic rhinoplasty in America is then broken down further into broad sub classification such as African American, Asian, Hispanic, etc. The terminology regarding the ethnic rhinoplasty, however, is comparative to a White standard. Patel and Daniel' classification of the Indian American rhinoplasty concludes by stating that, "In general, Indian American women have a shorter nose, with a more acute nasolabial angle, and a wider alar base in comparison with North American white women" (Patel & Daniel, 2012). Boyette and Stucker state in their analysis of the African American rhinoplasty that, "the skin is typically thick with an abundance of subcutaneous fibrofatty tissue" and that, "the nasal spine us also less prominent [than the white nose], which translates to even less tip projection" (Boyette & Stucker, 2014). Both of the previous articles preface with the intention to classify types of rhinoplasties found within their respective ethnicities and present effective treatments, yet the analysis is often based around the structure of the 'typical' White nose instead of being based solely on the requests of the patients. The widely accepted understanding, within the field of cosmetic surgery, that 'ethnic' patients desire an ideal that is absent of a White beauty standard, makes the comparisons to a White nose seemingly unnecessary. If the White nose is used more so as a central reference point to describe the classifications of all ethnic noses, it is not clear that defining rhinoplasties based on ethnicity is an efficient approach to treatment.

Classifications of noses within an ethnic group appears to be based on the desire to provide more targeted treatment to racial minorities in America, but the descriptions of each classification often resemble that of other ethnicities entirely. Patel and Daniel state that, "the category 2 Indian American rhinoplasty is often similar to variations of the Persian nose" and "the category 3 Indian American rhinoplasty patient is similar to patients of other ethnic groups, ranging from Asian to African American patients" (Patel & Daniel, 2012). In Daniel's classification of the Hispanic nose, the Type I (Castilian) nose treatment is 'similar to the average White rhinoplasty" (Daniel, 2003). A study by Ofodile and James even found that, "contrary to popular myth, [the alar cartilage in blacks] is similar in size to that in Whites" (Ofodile & James, 1997). The amount of crossover, in terms of nose categorization, suggests that (1) ethnicity is likely not a good classifier of nose structure or subsequent rhinoplasty treatment and that (2) the White nose is equally unequipped to serve as the cosmetic standard for ethnic rhinoplasties. While ethnic classifications serve to enhance the treatment of emerging ethnic groups within plastic surgery, they may instead create barriers for patients to receive ideal treatment by placing them into classes based on social constructs.

In nearly every article that focuses on ethnic rhinoplasty, the discussion of "preserving" ethnicity is explicitly stated as a requirement. Similarly, it is clear that patients desire a nose that is unique to their face, so what does it mean to preserve a patient's ethnicity? The classic example is that a White nose on a non-White patient would look ridiculously out of place, but the interconnectedness of nose structures between ethnicities suggests that this may ultimately be a fitting treatment for some. More likely, the example is meant to describe a new nose that rivals the fundamental structure of the original nose, undeniably accompanied with the feared botched look. In this case, ethnicity is neither the problem nor the solution. The patient was treated with a nose that was not unique or fitting to their face, regardless of their ethnicity. Defining the patient's ethnicity beforehand would not have corrected this hypothetical cosmetic mishap, because the scenario would apply equally to a White patient receiving a fundamentally different nose. When surgeons and patients speak about preserving ethnicity, I would argue that they are vying for a rhinoplasty that takes the patient's aesthetic proportions into account. A cookie-cutter one-size-fits-all nose

is no longer applied in practice, so it seems disingenuous to suggest that that is the default if treatment is no longer based around ethnicity. The effectiveness of ethnic classifications may be questionable, but the engagement between cosmetic surgery and ethnic minorities in the United States is continuing to grow.

As ethnic procedures become more popular and the demographics of America rapidly diversifies, it may be time to institute a classification system that can be applied to all patients based on the physical characteristics relevant to rhinoplasty. Describing parts of the nose as "weak", "under projected", "under protonated" and "ill-defined" establishes an innate hierarchy within the terminology, where the White nose sits at the top. These comparative distinctions provide little insight into an appropriate plan for treatment because patients are not seeking a "White" nose and oftentimes patients are seeking to correct a specific aspect of their nose such as increasing the height of the nasal bridge or increasing tip definition. By defining the nose in terms of the patient's request, then terminology like "under projected" no longer evokes a white counterpart, but rather the goal of the procedure itself. In other words, the pre-operation nose is only described in comparison to the ideal nose. Additionally, creating a universal rhinoplasty classification system across ethnicities may be able to better accommodate patients who do not hold an ethnic identity that is congruent with their nose classification. As stated before, the classifications across ethnicities tend to mix together, to the point where classifications between ethnicities may hold more similarity than those within the same ethnicity. Instead of grouping patients by ethnicity, the universal system would be based on physical characteristics that are considered when conducting a rhinoplasty. Nasal bridge height and tip projection are already measured in quantitative units, so creating classification bins around these units would provide more accurate descriptors and lead to more accurate treatments. The argument for a new classification system is not one of semantics, but rather a need to more accurately define and treat a population that is blurring the lines between what it means to look like a certain ethnicity. As globalization continues, a classification system based on ethnicity may become more of a guessing game than one of medical diagnosis.

Further study is certainly needed to determine the effectiveness of ethnicity-based classifications. The claims of this thesis indicate that a patient's ideal self can be achieved through treatment that is based on structural characteristics, rather than ethnicity, but no universal classification system currently exists. A study of patient satisfaction would first need to generate this classification system, as defined by relevant structural components that guide cosmetic rhinoplasty treatment. Variables may include measurements of the nasal dorsum, tip complex, alar rims, and bony vault (Rohrich & Ahmad, 2016). Once the classifications are created, existing 3D imaging technologies commonly used in plastic surgery practices should be used to virtually alter a patient's face to include their ideal rhinoplasty. This ideal rhinoplasty should then be compared to the closest pre-existing ethnic classification and to the closest universal system classification. Patient satisfaction of the two new rhinoplasties should be measured. The results of this study will hopefully shed light on if (1) the measurements of interest strongly correlate to overall satisfaction, if (2) patients' ideal noses fall outside of their previously assigned ethnic classification, and if (3) patient satisfaction rates are significantly different between the two classification methods.

## Conclusion

The role of ethnicity within the plastic surgery treatment is a complex topic, but the rejection by plastic surgery patients of a singular beauty standard is clear. South Korean patients highlight fundamental differences in aesthetics as well as a history of beauty standards that predate western influence. In the United States, non-White patients equally reject a desire to look White, more so focusing on culturally-specific indicators of beauty. Through the use of cosmetic surgery, ethnic minorities in America are using plastic surgery as a means to reclaim beauty standards, co-opting an industry that was built around a White model of beauty. In this way, plastic surgery should not be viewed as a mechanism of oppression, but rather the opposite, a tool to achieve the ideal self. Cosmetic surgery patients have rejected the notion of conformity, rather in favor of self-improvement, so this outlook should be applied to how patients are classified for treatment. Ethnicity-based classifications have been shown to be imprecise, inefficient, and increasingly outdated in the treatment of ethnic patients. They implicitly create aesthetic hierarchy based on ethnicity

by comparing all patients to a White standard, and ethnic patients are grouped into broad categories based on factors not entirely relevant to surgery. Additionally, globalization is blurring the physical characteristics outlined in literature on ethnic features, requiring the need for a new classification system based on medically physiologically relevant characteristics. Based on the growing ethnic patient population and the industry desire to provide individualized care for all patients, the reclassification of the rhinoplasty appears to be a logical next step in improving care.

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**Differences in cellular responses using microporous annealed particle (MAP) hydrogels with varied chemical compositions**

(Technical Paper)

**Analysis of how self-image is generated through the use of cosmetic surgery**

(STS Paper)

A Thesis Prospectus Submitted to the

Faculty of the School of Engineering and Applied Science

University of Virginia • Charlottesville, Virginia

In Partial Fulfillment of the Requirements of the Degree

Bachelor of Science, School of Engineering

**Christian Hennessey Jenkins**

Fall, 2020

Technical Project Team Members

Kyle Limpic

On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

Signature _____ Date _____

Christian Jenkins

Approved _____ Date _____

Donald Griffin, Department of Biomedical Engineering

Approved _____ Date _____

Sean Ferguson, Department of Engineering and Society

## Introduction

Glottic incompetence (GI) is the partial paresis of the vocal cords, often diagnosed in geriatric patients, professional singers with overuse injuries, and patients who have complications from prolonged intubation (Onwordi & Al Yaghchi, 2020). As the vocal cords atrophy, they lose tissue volume and are unable to close during swallowing or vibrate appropriately for speaking. Patients often present with chronic bacterial lung infections from improperly swallowing and a whispery and raspy voice. Without proper treatment to regain volume loss, the risk of infection increases and vocal capabilities deteriorate. To combat this volume loss, we are synthesizing a microporous annealed particle (MAP) gel implant within various chemical backbones that promotes natural tissue growth without triggering an immune response.

Although our project is specifically focused on volumizing vocal folds, due to its functional application, the highly targeted injectability of MAP provides for a wide array of applications, including cosmetic surgery. MAP gel is different in structure as well as chemical and physical properties from the highly popular fillers used in plastic surgery, but I began to think about the evolution of plastic surgery over the past twenty years, and subsequently how the types of procedures performed have evolved with popular culture. I thought about if there was a uniform beauty standard trying to be achieved and if physical modifications could ‘de-racialize’ patients of color by removing or altering distinct facial features often shared by a population. I have a deep interest in medicine, tissue engineering, and how diverse populations interact with the medical field. In my research, I hope to understand how self-image is formed and transformed through the technology of cosmetic surgery and how this phenomenon varies among racial groups.

## Technical Topic

Hydrogels are a class of biomaterials that are characterized by their ability to absorb large amounts of water while retaining their structural properties (Highley et al., 2016). Hydrogels are generally monomers that are chemically or physically crosslinked in order to achieve the swelling of water and mimic human tissue. Currently, GI is treated using degradable fillers, most commonly Restylane (Pruett et al., 2020). Restylane is a nonporous hydroxyapatite with an elastic modulus similar to bone and known to trigger severe foreign body responses (FBRs) (Pruett et al., 2020). The lack of porosity in Restylane means that cells must break down the filler as they proceed into the injection site, which makes degradation properties dependent on the rate of cellular infiltration. The stiffness of the filler and lack of a natural cellular environment can ultimately lead to the identification of the implant as a foreign body by the immune system, leading to inflammation. Furthermore, natural tissue and vasculature is unable to penetrate Restylane, so when the filler degrades after 6 months, patients must receive new injections. Each procedure is followed by a three-day period of silence and the bone-like mechanical properties of Restylane produce a harsh raspy sound when the vocal cords vibrate during phonation (Pruett et al., 2020).

MAP gel is a porous hydrogel, meaning that as the polymer backbone is annealed with UV light, microscopic pores form throughout the gel, creating a scaffold (Griffin et al., 2015). The chemical and physical properties of MAP gel are highly controlled to match the mechanical properties of specific human organs while promoting cellular infiltration. Due to the porous nature of the material, the scaffold does not trigger a FBR (Griffin et al., 2015). The size of the pores allows for cells to immediately enter the gel following implantation and begin synthesizing extracellular matrix (ECM) necessary to promote natural tissue growth and vascularization. As the ECM lines the internal MAP scaffold, the immune system cannot distinguish the gel from natural

tissue, so no immune response ensues. Furthermore, the physical properties are independent of cellular infiltration rates, so the rate of structural degradation can be optimized without affecting the physiologic response. The immune system also recognizes foreign objects by their shape and stiffness. Materials with defined edges or mechanical properties that do not match surrounding tissue will be marked as foreign and be broken down by immune cells. MAP gel's highly controlled physical properties allow for its formulation to be altered to match the native elastic modulus at the injection site and its amorphous shape allows for the gel to effectively hide from the immune system.

For our technical project, we will be synthesizing MAP gel using three different chemical backbones: polyethylene glycol (PEG), hyaluronic acid (HA), and gelatin methacrylate (GelMa). These polymer backbones will be compared on the metric of cellular infiltration rate, which is the key factor in determining the rate of natural tissue growth and vascularization throughout the scaffold. In order to identify the backbone as the only independent variable, we will control for physical factors such as pore size, particle size, and elastic modulus. The pore and particle size will be determined by the synthesis of GelMa since it is the least tunable material. Once the formulations are determined for each backbone, we will conduct an *in vivo* study by injecting the PEG-MAP, HA-MAP, and GelMa-MAP into the subcutaneous layer of a mouse model (Pruett et al., 2020). We will then image the tissue and run various assays to quantify cellular migration, collagen deposition, vascularization, cellular infiltration and degradation. The results will be compared to identify the best MAP backbone for this application.

My role is to analyze Instron elastic modulus results and correct the MAP formulation until the appropriate elastic modulus is reached. I will then conduct image analysis, analyze chemical assays, and complete a comparative analysis across all three backbones. This research is being

conducted under the guidance of Professor Donald Griffin in the Department of Biomedical Engineering at the University of Virginia.

## STS Topic

The stigma surrounding plastic surgery has been greatly reduced in the past few decades and the number of procedures has exploded in recent years (Adams, 2012). Celebrities and influencers are more transparent about their surgical operations, and cosmetic procedures have increased across every racial group and gender. As the field of plastic surgery begins to see an increase in diverse populations, it is vitally important that physicians are aware of their responsibility to provide patients with cosmetic changes that still reflect the individuality of the patient. Through the lens of both patients and physicians, this research will identify how ideas of self-form and determine how different racial groups interact with cosmetic surgery.

The origins of plastic surgery date back to World War I when physicians were presented with thousands of soldiers who were severely disfigured from trench warfare. After enduring highly stigmatized periods, plastic surgery has gained a massive clientele spanning throughout the western and eastern world, and more recently, has seen a dramatic increase in the number of non-white customers in the United States (Menon, 2017). This market boom, due to stronger purchasing power across all racial groups, has spurred the intense discussion on 'ethnic plastic surgery' in America (Menon, 2017; Sturm-O'Brien et al., 2010). The ethics surrounding procedures on non-white patients to reduce or alter physical characteristics that are commonly associated with their ethnic group (de-racializing) is a hotly debated topic that forces physicians to consider how to provide cosmetic alterations in a way that preserves the patient's identity (Adams, 2012). The concept of de-racialization through surgery is not new, but it may often be mischaracterized at the expense of patients.

Seoul, South Korea is currently the plastic surgery capital of the world, with approximately 50% of women in their 20s undergoing a procedure (Leem, 2016). The commercialization of plastic surgery has completely destigmatized the industry; surgical procedures are often given as gifts or recommended to friends (Marx, n.d.). Western media, however, has focused heavily on the perceived de-racializing of Korean patients through this medium, often attributing motivations to the attainment of a white beauty standard (Stone, 2013). This western perception of the Korean cosmetic industry is not entirely unfounded, but it is also strongly dismissed by Koreans as a reason for surgery (Leem, 2016; Stone, 2013). The most common procedures in Korea are the double eyelid surgery to produce a fold in the eyelid, skin whitening, and the rhinoplasty to reshape the nose (Leem, 2016; Marx, n.d.). Korean surgeons and patients alike cite an incredibly long history of Asian beauty standards that guide the popularity in procedure type, and reject the notion that whiteness is a contributing factor. Surgeons point to the rarity of double eyelids as a long sought-after trait, light skin as a traditional symbol of wealth, and note that the ideal Korean nose varies structurally and aesthetically from the typical Caucasian nose. Furthermore, Korean beauty standards include physical features that greatly differ from western ideals, such as less prominent cheekbones and narrow jaws (Leem, 2016; O'Connor, 2014). In terms of motivations for surgery, Koreans primarily cite employment and social benefits while attributing the rise in plastic surgery to the cultural importance of wholistic success (Leem, 2016). Patients and physicians in South Korea understand that the desire for facial modifications is not rooted in efforts to de-racialize, but rather to achieve a look that aligns with personal and professional goals. By viewing plastic surgery as a technology to achieve an ideal self, we can begin to understand how American patients are motivated in similar ways. Instead of ascribing procedures as 'ethnic', perhaps there needs to be a

better understanding that patients are seeking deeply personal and highly specific modifications to achieve their ideal self, rather than seeking a single beauty standard.

In the United States, a singular beauty standard is elusive as it has become increasingly more variable. Just 10 years ago, lip injections for bigger lips were not nearly the beauty staple they are today. The most common surgeries include breast augmentation and rhinoplasty, but a diverse consumer base has complicated the standard medical proportions surrounding procedures (Menon, 2017). By isolating the effects of each type of procedure by race, it seems unlikely that a uniform beauty standard would emerge. Perhaps the most common physical feature labeled 'ethnic' in American cosmetic surgery is the nose (Menon, 2017). Medical professionals agree that when reshaping a nose, the patient's ethnicity must be preserved, but this brings into question what it means to be a certain ethnicity (Sturm-O'Brien et al., 2010). Is it therefore possible to mute a patient's ethnicity entirely through surgery (Menon, 2017)? The idea of ethnicity being mutable is not a goal of plastic surgeons, but it must be considered when determining how to appropriately treat a patient (O'Connor, 2014). A Black patient and an Asian patient requesting a nose with more projection likely do not want the resemblance of a typical Caucasian nose, but rather a physical alteration specific to them and their identity. According to Chait and Widgerow, medical literature describing the ideal nose "has often led to patients being left with noses that look almost identical and bear no relationship to their other facial features, sex, or race" (Chait & Widgerow, 2000). This forces physicians to reject standard medical proportions and understand the ideal self that patients seek.

Through the co-production of science and technology, I hope to assess how social groups generate the perception of self with the existence of plastic surgery and how the evolution of cosmetic surgery has allowed patients to reconcile the three components of social identity: self-

image, self-esteem, and ideal self (Walker et al., 2019). Literature reviews are critical to my research on patient motivations and self-concept post-operation, but I also plan to survey plastic surgeons to identify how they determine and appropriately alter ethnic characteristics as well as identify underlying motivations for surgery among patients. Although patients are the direct recipients of cosmetic procedures, physicians also take on a primary role in regulating patient expectations during consultation and throughout the recovery process, therefore shaping the patient's self-image and ideal self (Leem, 2016). In order to understand how self-esteem interacts with physical alteration, it may be beneficial to analyze malpractice reports and postoperative satisfaction reports to identify trends for why patients' ideal self was not met (Ferraro et al., 2005; Schwitzer et al., 2015). Through this analysis, I plan to use trends among patient populations to determine how self-image is created through the use of cosmetic surgery.

## Next Step

It is clear that as the patient population for plastic surgery diversifies, both physicians and patients need to be cognizant of how physical modifications can affect self-image. As I look at self-image through the lens of ethnic social groups and technological advancements, it is important to consider the individuality of patient choices and the changes in perception of self that follows. In the following thesis, I plan to expand upon existing scholarship noting patient expectations over time, medical standards for defining proportions, and interviews with patients and surgeons, then collect qualitative data from cosmetic surgeons in the University of Virginia Health System to identify physician perceptions of patient self-image changes. Interviews with cosmetic surgeons will use a formal standardized interview protocol. I plan to focus mainly on procedures that alter facial characteristics, since these are often most commonly labeled as defining features of ethnic groups.

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