

Hair Research in 2017: A Look Back at 20 Research Papers that Influenced My Practice

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As 2018 unravels, I find it important to reflect on the year that has past. This is particularly true in the world of hair research where discoveries in both basic research and clinical research have either confirmed, refuted or opened new doors into how we think about hair loss.

I'd like to share with you research papers from 2017 that have shaped the field of hair loss.



1.

Preventing Chemotherapy Hair Loss

ARTICLE: *Nangia J, et al. Effect of a Scalp Cooling Device on Alopecia in Women Undergoing Chemotherapy for Breast Cancer: The SCALP Randomized Clinical Trial. Randomized controlled trial. JAMA. 2017*

WHY IS THE
ARTICLE
IMPORTANT?

Facilitated FDA
approval of
Paxman Device
in USA

2017 saw the FDA approval of the Paxman Cooling device for preventing hair loss during chemotherapy. Hair loss in patients undergoing chemotherapy has a major impact on quality of life. Some patients rate hair loss as one of the most negative aspects of their chemotherapy. Scalp cooling with various cold caps has emerged as a means to reduce the chances of hair loss during chemotherapy. In December 2015 the Dignicap was FDA cleared and this past year the Paxman cooling system received FDA clearance. IN June 2017, the Paxman Cooling Device was approved.

In the Paxman trial, patients receiving scalp cooling wore the device for 30 minutes before their chemotherapy treatment, for the duration of their treatment, and for 90 minutes following treatment. These women had stage 1 or 2 breast cancer and were receiving a broader range of chemotherapies. Out of the 95 patients who used the Paxman device, 48 (50.5 percent) lost less than 50 % of their hair (meaning no wig or scarf was needed, compared to 0 (0 percent) in the no cooling group. This study showed that scalp cooling is a highly effective method to reduce hair loss associated with certain types of chemotherapy.

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2.

Hair Follicles Direct Wounds to Heal Without Scars

ARTICLE: *Plikus et al. Regeneration of fat cells from myofibroblasts during wound healing. Science 2017.*

WHY IS THE ARTICLE IMPORTANT?

Represents a potential "paradigm shift" in the way we think about scars.

In 2017, new research from the University of Pennsylvania offers hope that one day it may be possible to heal wounds without scarring. The basic teaching of wound healing and surgery up to now had been that scars will form any time a wound, incision, cut or injury is made deep enough into the skin. This is due to cells known as myofibroblasts. Studies by Dr George Cotsarelis and colleagues have suggested that if myofibroblasts can be encouraged to become another cell type during wound healing, the possibility of a scar can be bypassed. The research showed that hair follicles in wounds can secrete a protein known as bone morphogenic protein or "BMP". BMP can trigger myofibroblasts to become adipocytes (a type of fat cell). Wound healing with adipocytes was shown to progress in a scarless manner.

This study is significant and represents a potential "paradigm shift" in the way we think about scars. The potential exists to help wounds heal without scar formation. More studies are needed to determine how to routinely make this happen in human skin.

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3.

Another Look at the Pull test

ARTICLE: McDonald et al. *Hair pull test: Evidence-based update and revision of guidelines. Journal of the American Academy of Dermatology* 2017; 76: 472

WHY IS THE ARTICLE IMPORTANT?

It changed how physicians examine the scalp of patients with hair loss

A 'pull test' has traditionally been one of the methods that hair specialists are taught to perform when examining the scalp. To perform the test, 60 hairs are lightly grasped between the thumb and index finger and gently pulled upwards. Removal of more than 10 % of the hairs in the bundle (i.e more than 6 hairs) has been traditionally viewed as a positive pull test and evidence that abnormal hair cycling may be occurring (i.e. telogen effluvium or other condition).

McDonald and colleagues from Ottawa, Canada performed a study revisiting this issues of what exactly constitutes a normal pull test and what limits should be set for abnormal. They studied 181 otherwise healthy individuals. The authors showed that for the vast majority of individuals, a pull test of 60 hairs extracts 0,1 or 2 hairs (97 % or more have 2 or less). Interestingly, the date the patient last washed their hair, did not influence the pull test result nor did the frequency of brushing the hair.

This 2017 study presents was simple and elegant and answered a lot important questions This well conducted study and it has renewed my interest in the pull test. It causes all clinicians to pause and consider a cut off of 3 rather than 6 when performing the pull test.





4.

The Immune System and Hair Growth

ARTICLE: *Ali et al. Regulatory T Cells in Skin Facilitate Epithelial Stem Cell Differentiation. Cell 2017.*

WHY IS THE ARTICLE IMPORTANT?

Changes the way we think about the hair follicle, and how it grows – giving new roles to immune cells

In June 2017, researchers at the University of California San Francisco reported an important new finding: without specific immune system cells called T regulatory cells (T regs), hair follicles do not grow properly.

T regulatory cells are important immune cells. Mice have them and so do humans. These immune system cells act as sort of peacekeepers of our immune system. In scientific terms, we say that these cells play a key role in ‘immune tolerance.’ They tell other immune cells of our body to stay quiet when the time is right to stay quiet and this helps prevent unnecessary allergies and autoimmune diseases. To study the role of T regulatory cells, the researchers developed a clever mouse model whereby T regulatory cells could be removed from the mouse whenever desired. In these studies, mice were shaved of hair and hair regrowth patterns were observed. Surprisingly, hair did not regrow after shaving.

There has now been a shift in thinking. Hair follicle stem cells, at least in mice, appear to listen to the commands of T regulatory cells to know when to grow – and when to stay quiet. Tregs are now understood to accumulate around hairs at the end of the hair growth cycle (in the telogen phase) and help direct hair follicle stem cells to make a new hair. Without Tregs, the growth phase (anagen phase) does not begin. This information could have direct relevance to humans and our understanding of a variety of hair loss conditions. It is well known from previous studies for example, that many of these genes that contribute to the condition alopecia areata are in fact genes that regulate T regulatory cells. In addition, other studies have shown that by supporting T regulatory cells in their functioning, it is possible to can help regrow hair in alopecia areata.



5-8. The Oral JAK Inhibitors for Alopecia Areata

- ARTICLE:** 5. Lui LY et al. Tofacitinib for the treatment of severe alopecia areata and variants: A study of 90 patients. *J Am Acad Dermatol.* 2017
6. Craiglow BG et al. Tofacitinib for the treatment of alopecia areata and variants in adolescents. *J Am Acad Dermatol.* 2017
7. Castelo-Soccio et al. Experience with oral tofacitinib in 8 adolescent patients with alopecia universalis. *J Am Acad Dermatol.* 2017
8. Ibrahim O et al. Treatment of Alopecia Areata With Tofacitinib. *JAMA Dermatol.* 2017.

WHY IS THE ARTICLE IMPORTANT?

Support the benefit of oral JAK inhibitors in treating alopecia areata

2017 saw the continued publication of articles supporting use of both topical and oral JAK inhibitors for treating alopecia areata. This includes the JAK inhibitory drugs tofacitinib (Xeljanz) and ruxolitinib (Jakavi, Jakafi).

To date, there have been six reasonably sized studies looking at the benefits of the oral JAK inhibitors. 2017 saw the publication of 4 of these. The message of all the studies has been the same: use of oral JAK inhibitors in patients with advanced alopecia areata helps, approximately one-half achieve cosmetically significant regrowth.





9.

Topical JAK Inhibitors for Alopecia Areata

ARTICLE: *Bayarat et al. Topical Janus kinase inhibitors for the treatment of pediatric alopecia areata. J Am Acad Dermatol 2017; 77(1):167-169*

WHY IS THE
ARTICLE
IMPORTANT?

Suggested
that topical
JAK inhibitors
may provided
benefit

As mentioned above, several studies in the last 2 years have shown benefit for the oral JAK inhibitors in treating alopecia areata. However, one must keep in mind that these drugs are not without potential side effects. For review see our handout

New data in 2017 suggested that topical JAK inhibitors may benefit patients with alopecia areata. Topical JAK inhibitors refer to specific formulations whereby the drug is mixed into a cream or other base and applied to the surface of area of hair loss rather than taken orally. These topical formulations have the potential to be safer than the oral formulations. However, it's not clear exactly how well the topical JAK inhibitors truly work. There have been a few published reports in the medical literature regarding the potential benefits of topical JAK inhibitors. A new study in 2017 reported the outcome of 6 individuals ranging in age from 4-17 who were treated with topical JAK inhibitors. 6 of the 7 individuals

had advanced forms of alopecia areata (totalis and universalis) and one had alopecia areata. Four patients (age 3, 5, 13 and 15) were treated with topical 2 % tofacitinib. 2 of the 4 patients had significant improvement of their scalp alopecia and 1 other had just a slight 20% improvement of his eyebrows. Two patients (age 4 and 17) were treated with topical 1 % ruxolitinib to the eyebrows. Neither one experienced eyebrow regrowth although one did experience eyelash growth when the medication was prescribed to the upper eyelid skin.

This study suggests that about one half of children with alopecia areata treated with topical JAK inhibitors may have some degree of benefit. This study is small and certainly a larger study is needed to confirm this. However, this study is encouraging given that these individuals had severe forms of alopecia areata to start with and treatment outcomes would therefore have been predicted to be worse.



10.

Genetics of Male Balding

ARTICLE: *Heilman-Heimbach et al. Meta-analysis identifies novel risk loci and yields systematic insights into the biology of male-pattern baldness. Nature Communications, 2017*

WHY IS THE ARTICLE IMPORTANT?

Outlined the complex genetics underlying balding and pinpoint several key associations including shorter height and possibly prostate cancer

Researchers at the University of Bonn recently performed an extensive study of over 20,000 men (10,000 with hair loss compared to 10,000 without hair loss). They concluded that many of the genes controlling male balding are also linked to being shorter in height and a few health problems such as cancer.

The researchers uncovered 63 genetic changes that increase a man's risk of developing early onset balding. These same genetic changes were associated with an increased likelihood of being shorter as well as developing prostate cancer.

This study confirms that hair loss is not an isolated phenomenon but rather controlled by genes that also determine one's height and various aspects of health.





11.

Genes and Balding: 287 Regions linked to Balding

ARTICLE: *Hagenaars SP et al. (2017) Genetic prediction of male pattern baldness. PLoS Genet 13(2): e1006594*

WHY IS THE ARTICLE IMPORTANT?

Outlined the complex genetics underlying balding and pinpoint several key associations including shorter height

In Feb 2017, a study from the UK nicely showed that male balding is far more complicated and many hundreds of genes contribute to balding in men. It identified 287 genetic regions linked to male pattern baldness. This large study examined data from over 52,000 men.

Of these 287 genetic regions, 40 were on the X chromosome (which men get from their mothers). This was confirmation that a man's mother does have an important impact on susceptibility to hair loss. The impact of the mother's side of the family was most important in men with early onset genetic hair loss in comparison to men developing hair loss in their late 30s and beyond. Using these 287 genetic regions, it was possible for researchers to give a given man a 'risk score' in order to predict men who were likely to have hair loss and men

who were not likely to have hair loss. For example, among those men with a low score, their risk for severe hair loss was only 14 %. Those men with a high score had nearly a 60 % chance of moderate to severe hair loss.

This study confirmed a similar finding as the Heiman-Heimbach et al. study in number 10 (see above) - namely that many of the genes regulating hair loss in men also give an increased chance for shorter height. The present study also uncovered additional associations including an association between male balding and

having a lower risk of bipolar disorder. This is an exciting study and builds on previous studies which identified only a limited number of genes. This data may improve our ability to predict and treat genetic hair loss in men.

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12.

Beard Alopecia and the Relationship to Scalp Alopecia

ARTICLE: *Saceda-Corralo D, et al. Beard alopecia areata: a multicentre review of 55 patients. J Eur Acad Dermatol Venereol. 2017.*

WHY IS THE ARTICLE IMPORTANT?

Gives a much better appreciation of the markedly increased risk of scalp alopecia areata in patients presenting with beard alopecia areata

Alopecia areata is a relative common autoimmune condition affecting up to 2 % of the world. Beard and facial alopecia is particularly concerning to many men as it can be challenging to camouflage. A frequent question from patients with beard alopecia areata is „how likely is it that I will eventually develop patches on my scalp?“ Another wonderful multicentre study back in January 2017 helped answer that question. The researchers studied 55 men with beard alopecia and followed them for at least one year. In the study, 45 % of males developed scalp alopecia over the follow up period. Most who did develop AA (80%) did so in the first 12 months. The conclusion from the study was that a significant proportion of males with beard AA do in fact develop patches of scalp AA warranting long term follow up for these patients.



13.

Sunscreen Use and the Risk of Frontal Fibrosing Alopecia

ARTICLE: *Kidambi AD et al. Frontal fibrosing alopecia in men: an association with facial moisturizers and sunscreen. Br J Dermatol 2017.*

WHY IS THE ARTICLE IMPORTANT?

Although controversial, this study offered the world one of the first 'potential' environmental factors implicated in FFA

This is a controversial topic but this study (as well as an earlier 2016 study of FFA in women by the same authors) has caught the attention of many. A study by Kidambi et al examined factors associated with frontal fibrosing alopecia in men. The study compared how 17 men with FFA and 73 men without FFA responded to a lengthy survey. FFA is relatively rare in men but information on a link to sunscreen use was important to investigate given the possible role among women. Interestingly, a much greater proportion of men with FFA reported using sunscreens (as well as facial moisturizers) at least twice weekly compared to men without FFA. Specifically, 35 % of FFA patients reported such sunscreen use compared to just 4 % of men without FFA.

We have a long way to go to definitely prove sunscreens have a definitive role in how FFA developed. But two studies now (one in men and one in women) have described potentially the first environmental factor implicated in the way FFA develops. An environmental factor is certainly thought to be responsible given that FFA was relatively unheard of 20 years ago. There are more good studies that are needed.



14.

Finasteride and Persistent Erectile Dysfunction (PED)

ARTICLE: *Kigiradze et al. Persistent sexual dysfunction in men exposed to the 5 alpha reductase inhibitors finasteride or dutasteride. PeerJ 2017*

WHY IS THE ARTICLE IMPORTANT?

The very first reasonably well conducted study to examine the topic of persistent side effects in finasteride users. Supports that persistent sexual dysfunction after stopping finasteride could be a bona fide side effect of the drug.

Finasteride is an oral medication that is FDA approved for treating male pattern hair loss. It is well known that sexual dysfunction is a potential side effect of finasteride that occurs in less than 2% of male users. Recently concerns have arisen that these side effects may be persistent in some - even after stopping the drug. A 2017 study by Dr Belknap and colleagues from Northwestern University in Chicago has given the first solid attempt at quantifying the risk of persistent sexual dysfunction with men using the hair loss drug finasteride. Studies to date and clinical trials in the 1990s first showed that sexual dysfunction was possible with finasteride. However, these studies did not show that men using these drugs experienced any residual side effects if they chose to stop the drug. In fact, some of the clinical trials showed that side effects often went away even if men kept taking the drug.

Belknap and colleagues examined a large database of patient records and looked for patients who had used finasteride and dutasteride and who also reported erectile dysfunction, decreased libido. In addition - the authors looked at the proportion of patients experiencing persistent sexual dysfunction or „PED“ (defined as erectile dysfunction occurring more than 90 days after stopping the drug).

The main messages of the study were that men using finasteride 1 mg have an approximately a 1 % chance of experiencing persistent erectile dysfunction (PED). About 1 in 3 young men who ultimately do experience erectile dysfunction using finasteride will experience persistent erectile dysfunction - and this can last several years (average 3.7 yrs in the study). The longer one is using these medications the greater the risk of PED.

This study is important. We are moving away from wondering whether or not PED is real or not to now wondering what exactly is the risk (is it actually much less than the study quoted? ... or is it much more?). The concept of PED is here to stay. Moreover, I do feel it is important to advise patients considering finasteride about these issues and to advise patients who are currently on these medications that these issues can still occur in users despite lack of any sexual problems at present.

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An ideal study would be a randomized double blind placebo controlled study over 5 years. That has never been done. And likely never will be given the challenges, costs, etc. This would help us sort out the magnitude of risk.



15.

New Avenues for Treating Lichen Planopilaris

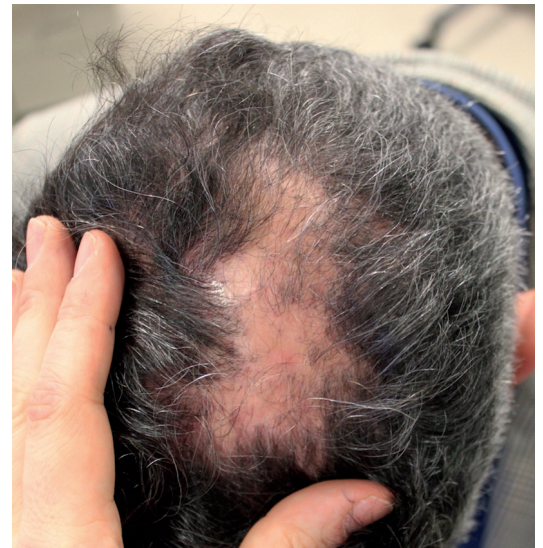
ARTICLE: *Strazzulla LC, et al. Novel Treatment Using Low-Dose Naltrexone for Lichen Planopilaris. J Drugs Dermal 2017*

WHY IS THE
ARTICLE
IMPORTANT?

Opens new
avenues for
further study in
LPP

Naltrexone is a medication that was approved in 1984 (at a dose of 50 mg) for treating addiction to opioids. Subsequently, it was shown that low doses rather than high doses sometimes have a remarkable effect on the immune systems. This opened the door to trying to better understand the benefits of low dose naltrexone (LDN). Studies have shown that LDN can help people respond better to many immunological conditions including HIV, cancer, and autoimmune diseases like lupus, Crohn's disease, multiple sclerosis. It has also been used in chronic pain. New evidence suggested benefit in lichen planopilaris as well. A very small study published in November 2017 suggested that LDN at a dose of 3 mg can reduce the signs of symptoms of this scarring alopecia. Side effects were not noticed.

It is currently thought that our internal opioid and endorphins have a key effect on the immune system. Various immune system cells are known to have opioid receptors on their surface. It is the ability to block opioid receptors in the body between 2 am and 4 am that is proposed to give the beneficial effects. Blockade in this manner lead to changes in the immune system and increase in the body's endorphin and enkephalin levels. These are powerful modulators of the immune system.





16.

Retinoids for Frontal Fibrosing Alopecia

ARTICLE: *Rakowska A, et al. Efficacy of Isotretinoin and Acitretin in Treatment of Frontal Fibrosing Alopecia: Retrospective Analysis of 54 Cases. J Drugs Dermatol. 2017.*

WHY IS THE
ARTICLE
IMPORTANT?

Opens new
avenues for
further study of
retinoids in FFA

Frontal fibrosing alopecia („FFA“) is an autoimmune disease that mostly affects women. It is classified as a „scarring“ hair loss condition and hair loss is often permanent for many women. A variety of treatments are available including topical steroids, topical calcineurin inhibitors, steroid injections as well as oral treatments like finasteride, doxycycline, hydroxychloroquine and isotretinoin.

A new study from Poland set out to compare benefits of finasteride and „retinoids“ (isotretinoin and acitretin) in women with FFA. The study included 29 women who were treated with a dose of 20 mg isotretinoin, 11 women treated with 20 mg acitretin and 14 treated with oral finasteride at a dose of 5 mg/daily. Interestingly, 76% of patients treated with isotretinoin, 73% of patients treated with acitretin, and 43% of patients treated with finasteride had their disease halted over a 12 month observation period.

This study is small and should be interpreted with caution for this reason. Nevertheless it is interesting and points to a potentially valuable role for retinoids that we really don't seem to see with classic lichen planopilaris (a closely related condition). The data in this present study however do not match other much larger studies of



finasteride use in FFA which have suggested that a much higher proportion of FFA benefitted from use of this drug. For now, this study provides us with evidence that retinoids can benefit some patients and should be at considered. Many women with FFA do have a tendency for increased cholesterol levels and the use of retinoids can significantly worsen this so caution and monitoring are needed.



17.

Seasonal Shedding: New Study Points to Summer

ARTICLE: *Hsiang EY et al. Seasonality of hair loss: a time series analysis of Google Trends data 2004 to 2016. British Journal Dermatology 2017.*

WHY IS THE ARTICLE IMPORTANT?

Reminds us of novel ways to harvest clinically relevant epidemiological data from the internet and reminds us of this important and too often forgotten concept of seasonal shedding.

A study from October 2017 in the British Journal of Dermatology suggests that humans shed more in the summer months. In fact, the order of most likely periods to have increased shedding is Summer followed by Fall followed by Winter. Spring was a time of least shedding. What made this study interesting to me was its design because it looked at Google Trends over time. Searches for „hair loss“ were found to fluctuate according to season. Seasonal shedding is important to remember. If one starts a treatment in Fall and notice by Spring things are better... one must ask if the treatment did it or would the hair have just gotten better anyways on account of it being Spring.



18.

Gynecomastia in Men using Finasteride and Dutasteride

ARTICLE: *Hagberg KW et al. Risk of gynecomastia and breast cancer associated with the use of 5-alpha reductase inhibitors. Clin Epidemiol. 2017*

WHY IS THE ARTICLE IMPORTANT?

It quantified the risk of gynecomastia in users of finasteride and dutasteride.

It is well known that finasteride and dutasteride can cause enlargement of breast tissue in men. This phenomenon is known as 'gynecomastia'. It is postulated that hormonal changes that accompany the reduction in DHT (particularly a small 13 % increase in estrogen) may be partly responsible. A new study from February 2017 looked at the risk of gynecomastia in men using finasteride for prostate enlargement. The authors used the UK's Clinical Practice Research Datalink (CPRD) to perform a case control study examining the risk of gynecomastia in individuals using finasteride compared to those who did not use. The researchers showed that there was a three-fold increased risk of gynecomastia in men using finasteride. A five-fold increased risk of gynecomastia was seen with dutasteride.



19.

The Role of Vitamin D in Alopecia Areata

ARTICLE: *Bhat YJ et al. Vitamin D Level in Alopecia Areata. Indian J Dermatol. 2017 Jul-Aug.*

WHY IS THE ARTICLE IMPORTANT?

This study adds to the growing body of evidence showing the vitamin D plays a role in alopecia areata. Vitamin D levels should be checked in these patients.

25-hydroxy-vitamin D is the best test for vitamin D status. Several previous studies have explored whether patients with alopecia areata have lower vitamin D levels. A new study compared vitamin D levels in 50 patients with AA compared to 35 age matched and sex matched controls. 25-hydroxy-vitamin D levels were lower in patients with AA being 16.6 in the AA group and 40.5 in the control group. In addition, patients with more severe AA had lower vitamin D levels than those with less severe AA. Also, those with more patches of AA had lower levels than those with fewer patches.



20.

Hormone Changes in LPP and FFA

ARTICLE: *Ranasinghe GC, et al. Prevalence of hormonal and endocrine dysfunction in patients with lichen planopilaris (LPP): A retrospective data analysis of 168 patients. J Am Acad Dermatol. 2017.*

WHY IS THE ARTICLE IMPORTANT?

Opens the way to further studies of hormonal changes in these conditions. Based on this study, I believe that it is important to assess hormone levels in women with these scarring alopecias.

In February 2017, the Cleveland clinic published study that showed that hormone abnormalities can be common in lichen planopilaris (LPP) and frontal fibrosing alopecia (FFA). A proportion of patients with LPP were found to have „androgen excess“ (increased levels of the male hormones). However there was a portion of patients with FFA that were shown to have „androgen deficiency.“ This did not prove to be true of everyone - but was a trend seen in a large proportion. These results were surprising, especially when considering that antiandrogens are helpful in FFA. It may however provide insight into differences between LPP and FFA. More studies are needed. For now, I feel that it is important to assess hormone levels in women with these scarring alopecias.