Fagron TrichoTest™

Scientific base of pharmacogenetic test to personalize hair loss treatment

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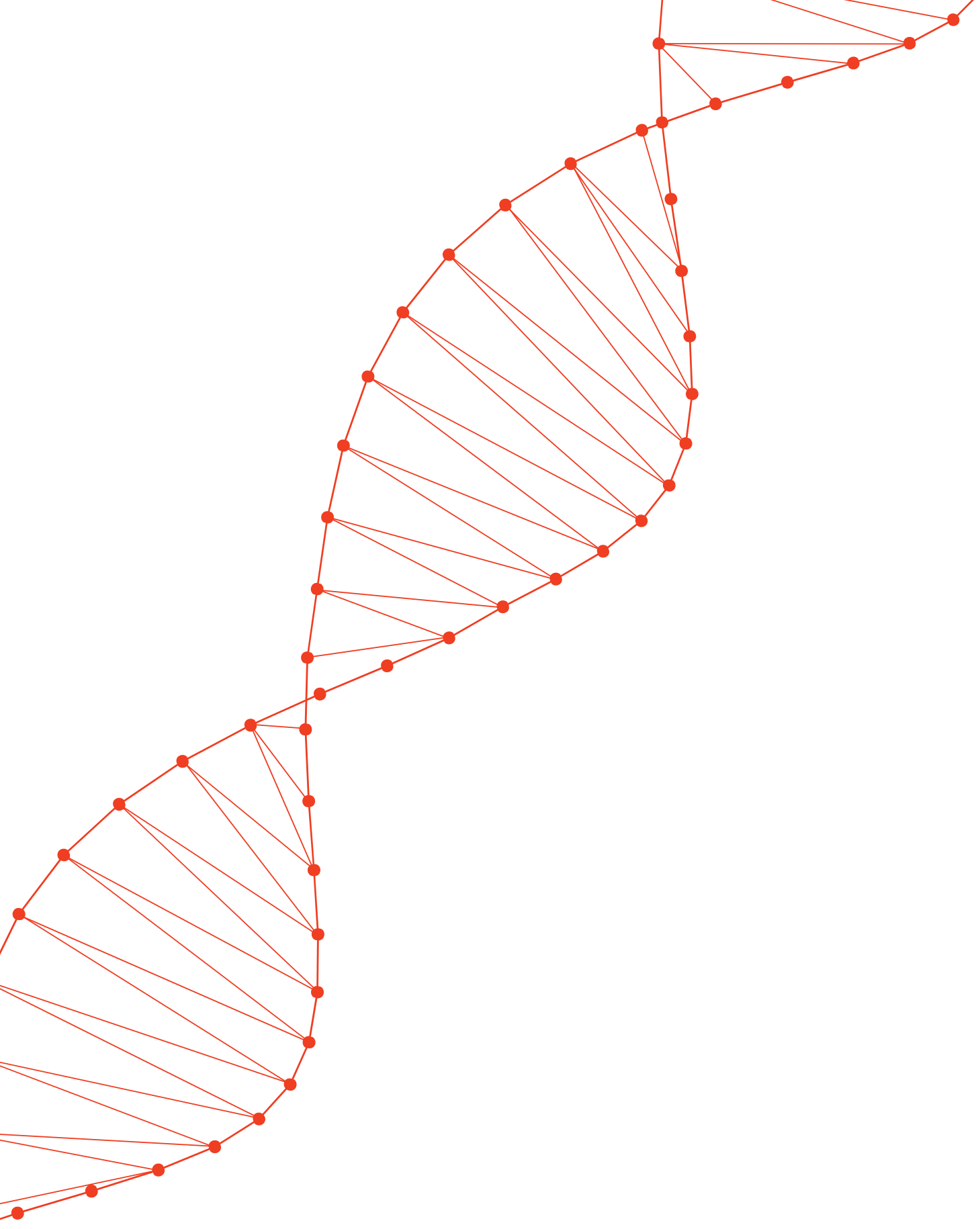
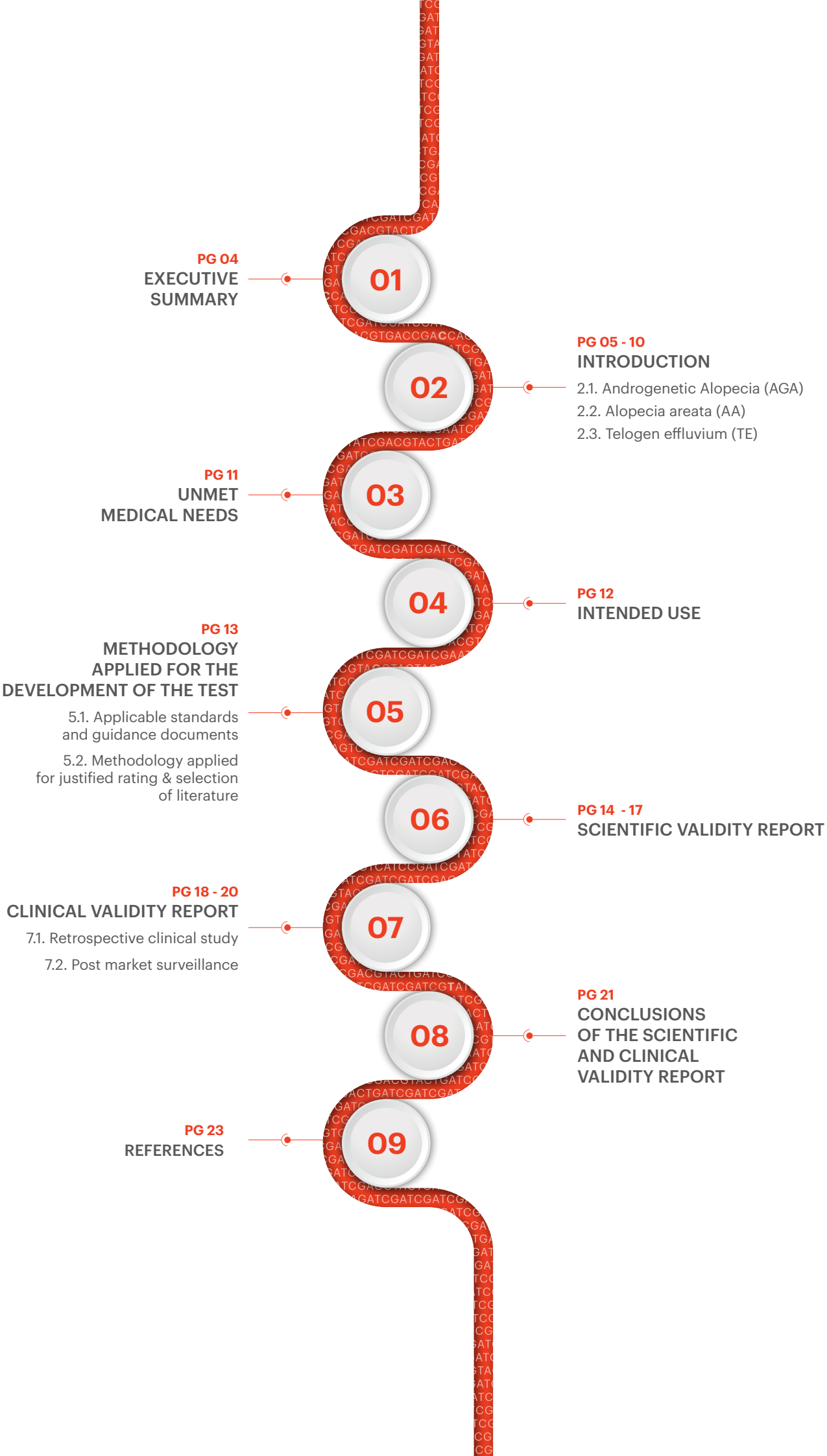
Fagron genomics





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01 EXECUTIVE SUMMARY

Fagron TrichoTest™

is a pharmacogenetic test that determine whether a male or female subject having androgenetic alopecia, alopecia areata or telogen effluvium is likely to be responsive to administration of specific hair loss treatments.

In its current version, the test analyses 16 genetic variations in 13 genes, used as biomarkers for predicting patient response prior to therapy.

Type and grade of alopecia, current medication, pathologies, intolerance, allergy, physiological and emotional stress are taken into consideration through a questionnaire. The **Fagron TrichoTest™** algorithm combines genetic data with relevant patient's anamnesis and possible contraindications to select the most appropriate vehicles and active pharmaceutical ingredients.

The following dossier, intended for prescribers, aims to deepen their understanding of **Fagron TrichoTest™** for an optimal patient support. After an overview on androgenetic alopecia, alopecia areata, telogen effluvium and associated treatments, this dossier describes the scientific basis of the test and its clinical evidence.

02 INTRODUCTION

Hair is considered an essential part of most people's identity and for many hair loss or irregular hair growth can have a significant impact on their psychological health. A hair growth cycle consists of growth (anagen), involution (catagen), and rest (telogen). Most people lose 50 to 100 hairs per day as part of this natural cycle. Alopecia is an abnormal hair loss that can occur anywhere on the body, but most commonly affects the scalp and is caused by an interruption in the hair growth cycle, whether due to age, autoimmune conditions, or stress. Common types of scalp alopecia include androgenetic alopecia, alopecia areata, and a thinning of hair known as telogen effluvium.

2.1. Androgenetic Alopecia (AGA)

Androgenetic Alopecia (AGA), also known as pattern hair loss, pattern alopecia or common baldness, is the most common type of progressive hair loss in both men and women. Although AGA is regarded more as a physiological condition than a disease, the psychological impact of hair loss can be profound and there is a significant association between AGA and life-threatening conditions, such as coronary artery disease and prostate cancer.

Incidence and prevalence of AGA depend on age and race. Based on the little prevalence data available, we know that up 30% of Caucasian men will have AGA by the age of 30, up to 50% by the age of 50, and 80% by the age of 70[1]. Other ethnic groups are less affected than Caucasians. AGA is known to be androgen-dependent and higher levels of serum testosterone are associated with increased risk. Thinning of the hair usually begins between the ages of 12 and 40 years in both sexes, and its natural course may be either slowly or rapidly progressing[2]. Factors that may accelerate progression include androgen metabolism, inflammatory scalp disorders, and lifestyle.

Figure 1. Androgenetic Alopecia.

AGA treatment

Alopecia treatment may simply involve accepting the condition, which can also include shaving one's head. Otherwise, common medical treatments for AGA include inhibition of Dihydrotestosterone (DHT) synthesis via 5AR inhibitors such as finasteride and dutasteride; inhibiting the downstream effects of androgen receptor activation with prostaglandin analogues such as bimatoprost or latanoprost, or medications that modify hair cycle dynamics such as minoxidil[3].

FDA-approved treatments: Currently there are only two FDA-approved drugs, which are included in most of the consensus treatment algorithms for AGA (see below): minoxidil and finasteride.

Topical minoxidil 2% and 5% (w/v) are FDA-approved in men, while a 2% topical solution and a 5% topical foam are approved for women. Topical minoxidil increases hair linear growth rate, increases fiber diameter, prolongs anagen duration and shortens telogen thus causing the quiescent hair follicles to enter prematurely into the anagen phase. Minoxidil is a prodrug, converted in the hair follicle outer root sheath to minoxidil sulfate by the enzyme sulfotransferase (SULT1A1). Minoxidil sulfate is a known activator of the ATP-sensitive potassium channel, thus displaying vasodilatory effects that increases the duration of the anagen phase and induces angiogenesis surrounding hair follicles. But it should not be discontinued due to post-minoxidil induced hair loss.

Finasteride 1 mg daily is FDA approved for the treatment of male AGA and is not indicated in women. It is effective in preventing androgen-dependent miniaturization of hair follicles by competitively inhibiting 5-alphareductase (5AR) type 2 enzyme, in turn preventing conversion of testosterone to DHT. Finasteride 1 mg treatment can lower serum and scalp DHT levels by 60% and results of 10-year follow-up studies confirm significant durable increases in hair growth at this dosage. However, the clinical response to finasteride varies considerably. While finasteride arrests hair loss in over 95% of men, only 66% achieve moderate hair regrowth and 5% marked hair regrowth.

Alternative treatments and combinations: Dutasteride is an alternative therapeutic option for men with AGA who show no clinical response to finasteride. Dutasteride inhibits both type 1 and type 2 5AR. Dutasteride is threefold more efficacious at inhibiting type 1 5AR and a hundred-fold more efficacious at inhibiting type 2 5AR than finasteride[4]. Dutasteride 0.5 mg can decrease serum DHT levels by 90% and thus, provides greater suppression of DHT than finasteride. A multicentre prospective study of 110 male patients with AGA on dutasteride 0.5 mg for 52 weeks found it to be safe, tolerable and effective[5]. Dutasteride is approved for the treatment of male androgenetic alopecia in South Korea and Japan at a dosage of 0.5 mg per day, but it can only be prescribed as an "off-label" treatment for hair loss in the other countries.

Topical minoxidil can be used in conjunction with finasteride or dutasteride to augment regrowth. It is weakly soluble in solution and so only low concentrations can be formulated.

Oral minoxidil appears to be more effective than topical minoxidil due to the ability to titrate the dose. Regrowth with both topical and systemic minoxidil is proportional to sulfotransferase activity thus agents that increase sulfotransferase, such as tretinoin enhance the regrowth effect of topical Minoxidil while agents that reduce it, such as aspirin reduce minoxidil efficacy.

Combination therapies with minoxidil have shown promising results for the treatments of female pattern hair loss (FPHL). A study showed that minoxidil and spironolactone, an aldosterone receptor blocker, in combination are an effective treatment option for FPHL[6]. Topical finasteride and minoxidil combination therapy was also effective in treating FPHL[7]. This therapy is limited to post-menopausal women due to the teratogenic effects of finasteride.

Figure 2. Hair loss stages.

Prostaglandins (PGs) play an important role in regulation of the hair cycle. PGD2 inhibits hair growth whilst PGE2 and PGF2a stimulate hair growth. Increased levels of PGD2 and reduced levels of PGE2 are seen in AGA affected scalp. A 24-week placebo controlled randomized trial including 16 male patients with AGA who applied PGF2a analogue latanoprost at 0,1% daily, found significant increases in hair density compared with baseline and placebo-treated areas[8]. Cetirizine is an antihistamine that decreases PGD2 production[9]. A pilot study of 85 patients with AGA evaluated the efficacy of topical 1% cetirizine applied daily for 6 months versus placebo. A significant increase in both total and terminal hair density was seen[10].

Extract from the berries of Saw Palmetto, a type of palm, induces a non-selective inhibition of 5AR type I and II resulting in a lower DHT uptake by the hair follicle. It also has the additional function of estrogen receptor activation which aids anagen maintenance and catagen normalization[11-14].

Alternative or adjuvant treatments: Topical treatment with 1 ml of a 0.1% melatonin-alcohol solution in women with AGA and diffuse alopecia resulted in a significant increase in detectable anagen hairs in the occipital and frontal areas after six months compared with placebo[15-17].

Ginseng intake can improve blood vessel health via modulation of vasodilation, oxidation stress, and pro-inflammatory cytokines[18,19]. The ginsenosides have been seen to promote hair growth via a mechanism similar to that of minoxidil[20-22].

Deficiency of essential nutrients and vitamins may represent a modifiable risk factor associated with the development, prevention, and treatment of alopecia[23]. However, there is still little evidence to support its benefits outside the scope of a potential deficiency.

Fagron TrichoTest™
selects active pharmaceutical ingredients (APIs), avoiding metabolic routes that can be inhibited.

2.2. Alopecia areata (AA)

Alopecia areata (AA), also known as patchy baldness or spot baldness, is a common form of immune-mediated alopecia in which an autoimmune attack on the proximal hair follicle (results in non-scarring hair loss ranging in presentation from circular patches on the scalp to total scalp or full-body hair loss. AA has a lifetime prevalence of approximately 2%[24].

Men and women are equally affected, with onset of symptoms occurring most commonly before age 30. The condition has a hereditary component 20% of patients possess at least one first-degree relative with AA.

AA is commonly perceived as a cosmetic, rather than medical, concern. However, substantial evidence exists describing the negative impact on quality of life, as the disease affects patients personally, socially, financially, and physically. The unpredictable course of the disease also makes it a mental struggle and AA patients are more often associated with depression and anxiety compared to the healthy population. Furthermore,

AA is associated with other concurrent diseases (comorbidities) including several autoimmune diseases including thyroid disease (hyperthyroidism, hypothyroidism, goiter ant thyroiditis), lupus erythematosus, vitiligo, psoriasis, rheumatoid arthritis and inflammatory bowel disease[24-25].

Figure 3. Alopecia Areata

AA treatment

In most cases, AA is a self-limiting disease with approximately half of cases remitting spontaneously within 12 months. Relapse is common, and for some patients it follows a chronic course. AA treatment remains challenging, with <20% of patients obtaining complete long-term hair regrowth. Treatment options include topical and systemic corticosteroids, topical tacrolimus, immunotherapy, and phototherapy, with variable efficacy particularly in severe AA[24,26].

The first-line treatment for most patients with AA is a local corticosteroid used as an immunosuppressive drug[27]. Corticosteroids can be also given as a pill or rubbed on the skin as an ointment, cream, or foam. Intralesional triamcinolone acetonide 5 - 10 mg/mL injected locally every 2 - 6 weeks results in localized hair growth in about 60% of treated sites.

Adverse effects include localized atrophy and hypopigmentation, and relapses often occur. Topical corticosteroids have limited benefit in patchy AA and can be associated with folliculitis.

Common corticoids for AA treatment include Hydrocortisone[27-28], Clobetasol propionate[29-35], Desonide[36], Betamethasone dipropionate[37-38], Fluocinolone acetonide[39], Prednicarbate often used in combination with Minoxidil and hydrocortisone to treat scalp pathologies[40-41] and Triamcinolone acetonide[42]. This latter is also used in the treatment of cicatricial alopecia[43] and Frontal Fibrosing Alopecia[44].

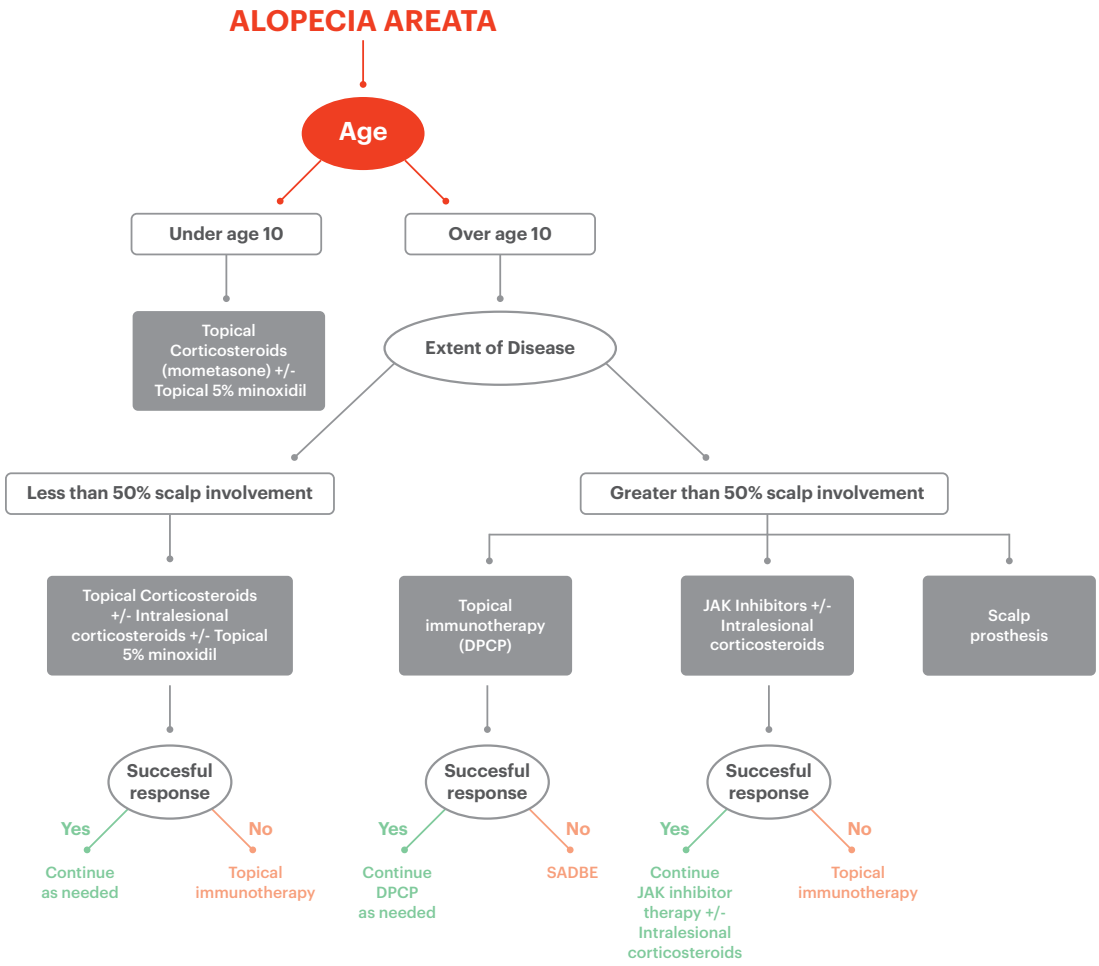


Figure 4. Treatment algorithm for the management of Alopecia Areata. (American Academy of Dermatology).

Tacrolimus, also known as FK506, is an immunosuppressive drug used for many years as an immunosuppressant in organ transplantation and in T-cell mediated autoimmune diseases. Tacrolimus is used in the treatment of AA to reduce inflammation[45-47]. Tacrolimus suppresses inflammation in a similar way to steroids, without causing skin atrophy or other steroid related side effects[48].

Contact immunotherapy is an effective treatment for some patients with alopecia areata. The application of a potent allergen to a small area on the scalp sensitizes the patient. The same allergen, in a concentration sufficient to induce a mild contact dermatitis, is then applied weekly. Contact allergens used in this treatment include dinitrochlorobenzene, squaric acid dibutylester and diphenylcyclopropenone, with diphenylcyclopropenone being most commonly used.

Older immunomodulatory therapies have also demonstrated limited efficacy in the treatment of AA. Methotrexate is immune-system suppressant that has been reported to be about 60 - 70% effective in treating AA, with better response rates occurring when used in conjunction with corticosteroids[49].

Finally, topical minoxidil therapy is usually an adjunct therapy for AA and tends to work better in less extensive cases.

2.3. Telogen effluvium (TE)

Telogen effluvium (TE) is a form of temporary hair loss, characterized by the thinning or shedding of hair, that usually happens after stress, a shock, or a traumatic event. There is usually a trigger that occurs 2 - 4 months before onset of hair loss. The cause may be endocrine, in the event of childbirth and hyper/hypothyroidism; nutritional, encompassing crash diets and vitamin A ex- cess; drug-related, most notably anticoagulants and b-blockers; and stress. TE can occur in people of any age, any gender, and any racial background. The exact prevalence of TE is not known, but it is considered to be quite common[50]. Studies have reported TE incidence in children to be around 2.7%[51]. A large percentage of adults experience an episode of TE at some point. TE can occur in either sex, though women have a greater tendency to experience this condition because of postpartum hormonal changes. Also, women are more disturbed by hair shedding than men and are therefore more likely to seek medical attention.

TE course may be acute or chronic. In Acute TE, hair loss generally occurs two to three months after the trigger exposure. In around 33% of the cases, the cause remains unknown. Acute TE usually undergoes remission in around 95% of cases. Hair shedding takes 3 - 6 months to cease, after which regrowth can be noted 3 - 6 months following the removal of trigger, but cosmetically significant regrowth can take 12 - 18 months.

If the causative event is identified by history and has been adequately treated, there is no further treatment required. If a hormonal or dietary imbalance or metabolic illness is present, hair growth will return after these factors are corrected. If a medication is the cause of the shedding, hair growth will restart after the medication is withdrawn, unless if this medication is essential for the patient's life.

Stress is one of the major contributing factors for TE and in this case psychological counselling is considered as the best and safest treatment. Chronic TE is a diffuse hair loss that persist for more than six months. It is characterized by abrupt, excessive, alarming, diffuse shedding of hair that runs a fluctuating course over several years. This condition predominantly affects healthy women in the fourth to fifth decade of life.

Figure 5. Telogen Effluvium.

TE treatment

Most of the cases of telogen effluvium are subclinical; therefore, its true incidence is not clearly known. After a diagnosis, it is essential to identify and remove the causative factors. Psychological counseling is important to address underlying anxiety or depression. Cosmetically, significant hair regrowth can take 12 - 18 months from the time of the removal of the trigger.

A few treatment options are also available, such as corticosteroids, minoxidil, and treatments such as CNPDA (caffeine, niacinamide, panthenol, dimethicone, and an acrylate polymer).

Topical minoxidil may be helpful because of its effect on prolonging the anagen phase[52]. However, there is still no sufficient peer-reviewed evidence to support the role of antioxidants or other supplements. Topical corticosteroids are employed by dermatologists in the treatment of chronic TE. Corticosteroids can be given systematically especially if chronic TE is the manifestation of underlying systemic disorder.

Fagron TrichoTest™ is a **pharmacogenetic test that determine whether a male or female subject having androgenetic alopecia, alopecia areata or telogen effluvium** is likely to be responsive to administration of specific hair loss treatments.

In its current version, the test **analyses 16 genetic variations in 13 genes**, used as biomarkers for predicting patient response prior to therapy.

03 UNMET MEDICAL NEEDS

The efficacy of the most recognized alopecia treatments is not absolute, and it requires at least a 4- to 6-month trial before noticing improvement and must be used indefinitely to maintain a response.

Although topical minoxidil exhibits a good safety profile, its efficacy in the overall population remains relatively low at 30 - 40%. While finasteride arrests hair loss in over 87% of men, only 11% achieve marked hair regrowth[53].

Due to the significant time commitment and low response rate, biomarkers for predicting patient response prior to therapy would be advantageous. Numerous polymorphisms defining potential response to alopecia treatments have been defined, but none of them are used on an individual basis in the clinical practice. Since SULT1A1 enzyme activity correlates with minoxidil response[54], Goren *et al.*[55] developed a colorimetric assay of SULT1A1 activity in plucked hair follicles to predict patient response to minoxidil.

A meta-analysis of the results from three studies (70 patients total) yielded an accuracy of 95.9% in ruling out non-responders to minoxidil[56]. This colorimetric minoxidil response test is registered by Follea International and commercialized in some clinics in Europe. SULT1A1*2 (rs9282861) genetic variant analysis could also be used for ruling out with a high accuracy non-responder to topical minoxidil treatment[57]. However, there is currently no evidence that this genetic test is commercialized or being used in clinical setting.

Fagron TrichoTest™

algorithm combines genetic data with relevant patient's anamnesis to select the most appropriate active pharmaceutical ingredients.

Alopecia treatment encompasses a wide range of treatment options and no inclusive genetic test for predicting patient response prior to therapy has been developed.

Type and grade of alopecia, current medication, pathologies, intolerance, allergy, physiological and emotional stress are taken into consideration through a questionnaire.

Fagron TrichoTest™ algorithm combines genetic data with relevant patient's anamnesis and possible contra-indications to select the most appropriate vehicles and active pharmaceutical ingredients (APIs) among a list of 11 vehicles and 62 APIs (Finasteride, Minoxidil, Latanoprost, 17-a Estradiol, Cetirizine Spironolactone, Triamcinolone acetonide, among others). There is currently no test comparable to **Fagron TrichoTest™** in the market.

The workflow is as follows:

1. The practitioner connects to Fagron's digital healthcare platform, enters patient data and completes the corresponding medical questionnaire.
2. Following the instructions provided with the kit, the practitioner collects the buccal swab sample and sends the sample for analysis to an authorized laboratory.
3. Once the patient questionnaire has been completed and the genetic data available, the reports can be viewed and downloaded from a secure personal area. Our digital healthcare platform meets the required regulatory and data protection standards.

Our online **medical platform** is intended to be used exclusively by healthcare professionals (intended user) with the purpose of helping them in managing their patient's genetic tests. Involvement of a trained professional may prevent or diminish misinterpretation of results.

Treatment should be guided by an **individualized assessment** of potential benefits and risks and accompanied by a monitoring plan to optimize the benefit-to-risk ratio. To facilitate practician's work, test results are displayed in a comprehensible fashion so that they are self-explanatory.

The company also organizes **training sessions** for non-geneticist health care providers and offers support for helping them in interpreting the results. Customer requests or incidents are recorded, and customer's suggestions are used for the preparation of new versions.

04

INTENDED USE

Fagron TrichoTest™

is intended to assist health professionals in making patient-specific care decisions regarding the treatment or prevention of androgenetic alopecia, areata alopecia and telogen effluvium.

Fagron TrichoTest™ analyses 16 single-nucleotide polymorphisms associated with metabolic pathways predicting alopecia treatment responses and combines this data with relevant patient's anamnesis to recommend the most appropriate treatment. Genetic data are obtained from commercially validated biomedical assays performed on DNA extracted from buccal swab.

Fagron TrichoTest™ uses an automatized qualitative pharmacogenetic algorithm that predicts treatment responses and recommends the most appropriate alopecia treatment options in adult male and female populations affected by this condition. Outcomes include genetic results and personalised treatment formulas with suitable active ingredients and doses.

Genetic Factors
TrichoTest™ analyzes the most relevant variations for personalizing alopecia treatment.

Patient anamnesis
Current medication, pathologies, intolerance, allergy, physiological and emotional stress are also taken into consideration through a questionnaire.

05 METHODOLOGY APPLIED FOR THE DEVELOPMENT OF THE TEST

Fagron TrichoTest™ was developed by a multidisciplinary team of medical doctors, nutritionists, pharmacists, geneticists, and programmers, following highest quality standards. In particular, an expert team specialized in the curation of genetic variants reviewed each variant to ensure that selection, interpretation and impact of variants in the algorithms are based on the highest scientific evidence. Relevant patient's anamnesis (intolerances, diseases, medication, blood pressure, among others) that can affect algorithm outputs (recommended products, formulation) was taken into account through medical questionnaires elaborated by health professionals. The most authoritative resources on active pharmaceutical ingredients, dietary supplements, herbal medicines, and complementary and integrative therapies are used to define our algorithm outputs. Applied standards, guidance and methodology for selection of variants and supporting literature are summarized below:

5.1. Applicable standards and guidance documents

According to regulation (EU) 2017/746, all tests that provide information on the predisposition to a medical condition or a disease, such as genetic tests, and tests that provide information to predict treatment response or reactions, such as companion diagnostics, are in vitro diagnostic medical devices. Applicable standards and relevant guidance documents for **Fagron TrichoTest™** are as follows:

- Regulation (EU) 2017/746 on in vitro diagnostic medical devices.
- ISO 13485:2016 Medical devices - Quality management systems - Requirements for regulatory purposes.
- ISO/IEC 27001 - Information security management.
- IEC 62304 medical device software – software life cycle processes.
- ISO 14971 Medical devices - Application of risk management to medical devices.
- MEDDEV 2.7/1 rev 4 Clinical evaluation: Guide for manufacturers and notified bodies.

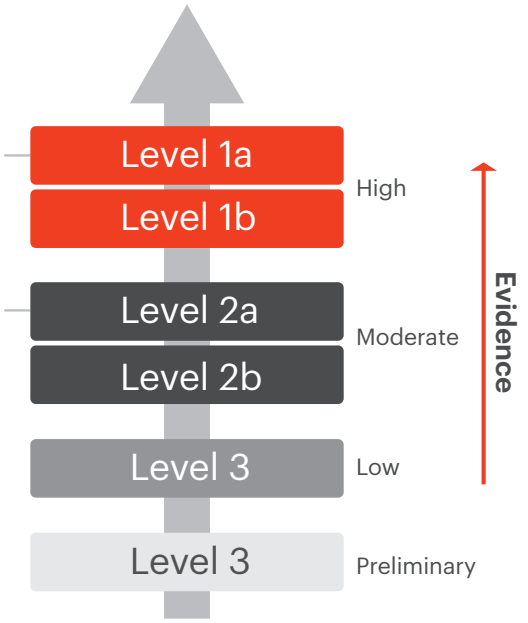
5.2. Methodology applied for justified rating & selection of literature

The following methodology was used for an objective and justified rating & selection of literature for **Fagron TrichoTest™** in vitro medical device development. Literature inclusion and exclusion was systematically justified.

Parameters such as number of study centres, multinational trials, methodological quality, journal impact factor and sample size were used to justify the inclusion or exclusion of peer-reviewed publications.

The following selection criteria was applied for classifying genetic variants:

- **Level 1A:** Annotation for a variant in medical society-endorsed or implemented in a major health system.
- **Level 1B:** Annotation for a variant where the preponderance of evidence shows an association. The association must be replicated in more than one cohort with significant p-values, and preferably will have a strong effect size.
- **Level 2A:** Annotation for a variant that qualifies for level 2B where the variant is within a Very Important known gene, so functional significance is more likely.
- **Level 2B:** Annotation for a variant with moderate evidence of an association. The association must be replicated but there may be some studies that do not show statistical significance, and/or the effect size may be small.
- **Level 3:** Annotation for a variant based on a single significant (not yet replicated) study or annotation for a variant evaluated in multiple studies but lacking clear evidence of an association.
- **Level 4:** Annotation based on a case report, non-significant study or in vitro, molecular or functional assay evidence only.



06 SCIENTIFIC VALIDITY REPORT

Fagron TrichoTest™ is a pharmacogenetic test that determines whether a male or female subject having androgenetic alopecia, alopecia areata or telogen effluvium is likely to be responsive to administration of specific hair loss treatments. In its current version, **Fagron TrichoTest™**, the software module analyses 16 genetic variations in 13 genes, used as biomarkers for predicting patient response prior to therapy.

Genetic traits and APIs covered by **Fagron TrichoTest™** are summarized below:

Prostaglandin metabolism

Although topical minoxidil exhibits a good safety profile, its efficacy in the overall population remains relatively low at 30 - 40%[54]. To observe significant improvement in hair growth, minoxidil is typically used daily for a period of at least 3 - 4 months Minoxidil is converted to its active form (minoxidil sulfate) by the hair sulfotransferase enzyme (SULT1A1)[54]. Since minoxidil response correlates with SULT1A1 enzyme activity[55], **rs9282861 SULT1A1** variant analysis (**level 1B**) could be used to predict minoxidil response[57-58]. If the patient is identified as "responder", minoxidil and agents known to increase sulfotransferase, and to enhance the regrowth effect of topical Minoxidil could be recommended[59]. The analysis of the **rs13283456 PTGES2** (Prostaglandin E synthase 2) analysis (level 1B) provides an indication whether a patient is likely to have low prostaglandin E2 production in the hair follicle that needs to be stimulated by minoxidil therapy[60,61-63].

The proposed mechanism behind the hair-growth-stimulating effect of minoxidil is through its stimulating effect of prostaglandin E2 (PGE2) synthesis[64]. Prostaglandins (PGs) are potent proinflammatory mediators and play an important role in modulating inflammatory and allergic immune responses. The role of prostaglandins in regulating hair growth and their dysregulation in AGA has been documented in the literature. For example, although PGE2 and PGF2a have been shown to stimulate hair lengthening in mice[65], PGD2 and its receptor GPR44 (also known as CRTH2) have been implicated as negative regulators of hair growth[66-68]. GPR44 expression is elevated in bald scalp compared to haired scalp of men with AGA[69].

Blocking the GPR44 receptor promotes hair shaft growth in cultured human hair follicles[69]. GPR44 rs545659 G polymorphism, resulting in an increased GPR44 mRNA stability[70], is associated with asthma and allergic sensitization[70-74]. Similarly, rs533116 GPR44 A polymorphism results in a higher level of GPR44 mRNA and is associated with asthma[75].

Higher GPR44 expression levels and increased responsiveness to its PGD2 ligand may be the biological basis for the association of this receptor with inflammatory and allergic immune responses[70,76]. **rs545659 GPR44** polymorphism (**level 1B**) in combination with **rs533116** (**level 1B**) provides information to healthcare providers about whether a patient is likely to benefit from treatments reducing prostaglandin D2 (PGD2) levels: cetirizine and prostaquinon, a phytocomplex derived from Nigella sativa seeds essential oil. Topical cetirizine is known for its anti-inflammatory properties and its ability to decrease PGD2 production[9]. It has been shown to significantly improve the initial framework of AGA with an increase in total hair density, terminal hair density, and diameter variation[8,77-78]. TE Patients treated with a scalp lotion containing 0.5% N. sativa seeds essential oil showed a significant increment of hair density and hair thickness. Thymoquinone is the most prominent constituent of Nigella sativa seeds essential oil[81] and has been shown to inhibit prostaglandin PGD2 production[79-82].

PGF2a analog latanoprost is FDA–approved and routinely used clinically to enhance hair growth of human eyelashes[83]. Latanoprost significantly increases the capillary density of bald patients[8,84-85]. PTGFR encodes the prostaglandin F receptor that binds to and mediates the biological actions of PGF2a. PTGFR polymorphisms are associated with positive and negative responses to latanoprost[86-88]. **rs10782665 PTGFR** allele variant T (level 2A) is related to a high probability of treatment efficacy with Latanoprost. Patients with the G have an increased likelihood of not having a positive response to Latanoprost[88]. Similarly, rs6686438 PTGFR allele variant T (**level 2A**) and **rs1328441 PTGFR** allele variant G (**level 2A**) are related with a higher efficacy in treatments with Latanoprost[88]. Analysis of these three PTGFR polymorphisms provides an indication to healthcare providers whether a patient has a high likelihood of having a positive response to Latanoprost or an increased likelihood of not responding to Latanoprost treatment, a quite expensive treatment option.

Inflammation

Intralesional corticosteroids are widely used in the treatment of alopecia areata[89]. Time to clinical improvement with triamcinolone acetonide, the most commonly used intralesional corticosteroid for AA ranges from 2 to 6 weeks. Topical corticosteroids applied to the scalp are less effective than steroid injections but might offer benefit in approximately 30% to 50% of AA patients[90]. Initial signs of improvement can take anywhere from 6 weeks to 3 months (up to 6 months in some). GR, also known as NR3C1, is the receptor to which cortisol and other glucocorticoids bind[91]. Several GR variants lead to altered sensibility of GR to glucocorticoids and are associated with resistance or sensitivity to corticosteroids[92-93]. **rs6198 GR** (Glucocorticoid Receptor) polymorphism (**level 1B**) is associated with resistance or sensitivity to corticosteroids[94-96] and provides a valuable information about response to corticosteroids. If the patient is identified as potentially resistant to corticosteroid, alternative treatment with tacrolimus, ginseng or melatonin. Tacrolimus is an immunosuppressive drug used in the treatment of alopecia areata to reduce inflammation[45-47]. Ginseng intake can improve blood vessel health via modulation of vasodilation, oxidation stress, and pro-inflammatory cytokines[19-20]. Topical treatment with 1 ml of a 0.1% melatonin-alcohol solution in women with AGA and diffuse alopecia resulted in a significant increase in detectable anagen hairs in the occipital and frontal areas after six months compared with placebo[15-17].

Androgenic effect – DHT metabolism

To observe significant improvement in hair growth, oral finasteride must be used daily for a period of at least 3 - 6 months. The overall effect of hair growth resulting of 5 years treatment with finasteride 1 mg is a stabilization of hair loss in 87% of patients, in whom only around 11% noticed an important hair regrowth[53]. Finasteride competitively and specifically inhibits the SR5DA2 enzyme[97-99], one of the two forms of steroid 5α-reductase responsible for the conversion of cortisol to dihydrocortisol and of testosterone to the more potent dihydrotestosterone (DHT). **rs523349 SRD5A2** polymorphism (**level 1B**) associated with active and less active forms of the SRD5A2[100-102] provides an indication about potential response to Finasteride treatment.

If the patient is identified as a potential "responder", finasteride and agents known to enhance treatment effect could be recommended: Zinc sulphate is a natural 5α-reductase inhibitor[103-106] shown to be effective in hair loss treatment[107-108]. Caffeine has vasodilator effects[109-110]. Ginseng intake can improve blood vessel health via modulation of vasodilation, oxidation stress, and pro-inflammatory cytokines[18-19]. The ginsenosides have also been discovered to promote hair growth through a mechanism similar to that of minoxidil[20-22]. Extract of Serenoa repens, commonly known as saw palmetto, is a botanical extract with antiandrogenic properties[11-12] used to treat AGA[13-14]. Dutasteride inhibits both forms of the steroid 5α-reductase[97,111]. **rs39848 SRD5A1** variant A (**level 2A**) is associated with a tendency to hirsutism in PCOS[112] and to lower levels of cortisol and higher levels of testosterone indicating a reduced enzyme activity[113]. rs39848 polymorphism provides an indication about potential response to dutasteride treatment and dosages to use. If the patient is identified as a potential "responder", dutasteride and agents known to enhance treatment effect could be recommended. CYP19A1 gene encodes the aromatase, responsible for the final step of the biosynthesis of estradiol and estrone. A decreased activity of aromatase leads to a decreased conversion of testosterone in estrogens and a higher conversion into DHT and results in hair loss[14,114-115]. **rs2470152 CYP19A1** allele variant G (**level 1B**) is associated to increased circulating estrogen levels and E2/T (estradiol/testosterone) ratios[116-120], a marker of aromatase activity[121]. rs2470152 polymorphism provides an indication to healthcare providers about potential response to 17-Estradiol treatments (stimulation of aromatase activity) and complementary (spironolactone) or alternative (ginseng, melatonin) treatments. Topical applications of lotions containing 17-estradiol have been shown to be effective to treat AGA[122-128]. Spironolactone is currently being used in dermatology as an antiandrogen[129] for the treatment of acne, diffuse hair loss in females, and hirsutism[130]. Topical treatment of spironolactone allows high penetration of the drug to the active site with the advantage of minimizing unwanted adverse effects[130] and has been shown to be effective in AGA treatment[6].

Topical treatment with 1 ml of a 0.1% melatonin-alcohol solution in women with AGA and diffuse alopecia resulted in a significant increase in detectable anagen hairs in the occipital and frontal areas after six months compared with placebo[15-17].

Vasodilatation and blood circulation

Growing evidence supports the hypothesis that the hair follicle cycling is associated with the remodelling of skin vascularization and perfusion[131-132]. Angiotensin-converting enzyme (ACE) is a membrane-bound, zinc-dependent dipeptidase that catalyses the conversion of angiotensin I to the physiologically active Angiotensin II, an extremely potent vasoconstrictor[133]. The ACE Insertion (I)/Deletion (D) Polymorphism affects ACE activity: Patients with allele D present increased ACE activity compared to patients carrying I[134]. Rs4343 A<G polymorphism is in near perfect linkage disequilibrium with ACE I/D in Europeans (A and G alleles marking I and D alleles, respectively)[135]. ACE polymorphism may influence numerous disparate conditions or phenotypes, including hypertension, Alzheimer and Coronary Artery Disease. **rs4343 ACE** polymorphism (**level 1B**) provides an indication to healthcare providers about the predisposition to increased levels of angiotensin II[134-137], a potent vasoconstrictor[133], and the possibility to treat with vasodilators commonly used for hair loss treatment: minoxidil[138], L-arginine[139-141], Caffeine[109-110], Ginkgo biloba[142], and Ginseng[19-21].

Collagen

Type I collagen is the most abundant collagen of the human body, representing up 75 - 90% of the collagen found in the skin, hair, nails, organs, bone, and ligaments. Type I collagen molecule is a heterotrimer consisting of two a1(I) and one a2(I) chains, which are encoded for by the COL1A1 and COL1A2 genes, respectively. Col1A1 is over-expressed in situations of androgenic alopecia[168]. **COL1A1 rs1800012** G>T (**level 2A**) results in increased COL1A1 gene expression[143-144] and has been associated with increased risk of osteoporosis[145] and of acute musculoskeletal soft tissue injuries[146]. The rs1800012 T allele is also associated with a higher 1 (I) to 2 (I) collagen protein ratio, which reflects the increased ratio of COL1A1 mRNA relative to COL1A2 and may result in an instability of collagen molecules[143].

If rs1800012(T) allele is detected, the **Fagron TrichoTest™** algorithm suggests the inclusion in the formula of commonly used composites associated with hair strengthening: cystine, silicon, adenosine. Cystine is crucial for hair strength, with its levels considered a surrogate measure for hair fragility[147]. Reduced levels of cystine have been associated with genetic disorders characterized by significantly in hair that is fragile, brittle, and fails to grow long[148-149]. Many nutraceuticals contain cysteine rather than cystine, as it is better absorbed than any other cysteine product. Oral administration of L-cystine, alone or in combination with other active ingredients, increases hair density and anagen rate[150-155]. Silicon prevents the loss of hair tensile strength suggesting that it has a structural effect on hair fibers[156]. Adenosine improves hair loss by stimulating hair growth and by thickening hair shafts[157-161]. Finally, methylsulfonylmethane (MSM) is a natural and highly absorbable source of sulfur necessary for the formation of keratin in nails, skin, and hair. MSM is a supplement recognized as safe (GRAS status) by the FDA for which small-scale studies have suggested benefits, particularly for treatment of skin, nail and hair conditions[162-163].

Insulin-like growth factor-I

Insulin-like growth factor-I (IGF-I) is a growth factor critically involved in promoting hair growth by regulating cellular proliferation and migration during the development of hair follicles[164-165]. Low circulating IGF-1 level is associated with hair loss[166-167]. To exert its biological effects, IGF-I must activate cells by binding to specific cell-surface receptors[168]. The type I IGF receptor (IGF1R) is the only IGF receptor to have IGF-mediated signalling functions[169]. **rs2229765 IGF1R** polymorphism (**level 1B**) provides an indication to healthcare providers about potential Insulin-like growth factor-I (IGF-I) levels and the need to treat with API increasing IGF-1 levels (Igrantine-F1 and TrichoXidil): Patients carrying at least one A allele have lower free plasma IGF-1 levels[170-172]. Cepharanthine is a natural product extracted from Stephania cepharantha with antiinflammatory properties. It is an approved drug used for more than 70 years in Japan to treat a variety of acute and chronic diseases[173]. Cepharanthine stimulates hair growth by increasing the production of IGF-1[174]. Igrantine-F1 (Fagron) is a substance isolated from Stephania cepharantha's dry extract containing at least 98% cepharanthin.

TrichoXidil™ is a phytocomplex with specific fractions of vegetable oils. Treatment with TrichoXidil ™ in the vehicle TrichoSol ™ promoted a reduction in 90 days of 37% of follicles in telogen phase and an increase of 29% of follicles in anagen phase. It significantly increased expression of growth factors KGF, IGF-1 and VEGF compared to controls (Fagron´s clinical study).

Metabolism of vitamins and minerals

Deficiency of essential nutrients and vitamins may represent a modifiable risk factor associated with the development, prevention, and treatment of alopecia[23, 175].

Vitamin A deficiency results in ichthyosis-like skin changes and sometimes causes telogen effluvium and the fragility of the hair. Vitamin C intake is crucial in patients with hair loss associated with iron deficiency[23]. Vitamin A and its derivatives (retinoids) are critically important in the development and maintenance of multiple epithelial tissues, including skin, hair, and sebaceous glands, as shown by the detrimental effects of either vitamin A deficiency or toxicity[176,177]. CRABP2, a cytosolic protein, moves to the nucleus upon binding of retinoic acid (RA) and thus is responsible for RA intracellular transport[178-180]. **rs12724719 CRABP2** AA (**level 1B**) is associated with higher RA concentration in blood and lower intracellular transport[181-182]. rs12724719 CRABP2 polymorphism provides an indication to healthcare providers about predisposition to inefficient intracellular transport of retinoic acid and the need to supplement with vitamin A derivatives, tocopherol and zinc. Retinol is one of the two forms of vitamin A available in the human diet. It has been suggested that vitamin A regulates both the hair cycle and immune response to alter the progression of AA[176,183]. Tretinoin, also known as all-trans retinoic acid, is a vitamin A derivative known to increase the percutaneous absorption of minoxidil and, therefore, to enhance the response of AGA to minoxidil[184-185]. The combined preparation minoxidil/tretinoin has been shown to be as safe as conventional minoxidil[59,186]. Tocopherol exerts an antioxidant action via the prevention of lipid peroxidation, similar to retinoic acid[187]. Supplementation with vitamin E has been shown to be beneficial for hair conditions[188].

Concomitant vitamin A and Zinc supplementation have been used for many years in the treatment of infammatory skin diseases[194] based on the observation that Zinc and vitamin A work in synergy for many functions in the body[195]. Zinc sulphate is also a natural 5α-reductase inhibitor[103,106] that has been shown to be an effective treatment option for hair loss treatment[104-105].

Biotin (vitamin B7) is an important cofactor that contributes to the normal functioning of enzymes responsible for carboxylation. BTD encodes the Biotinidase enzyme that allows the body to use and to recycle biotin. Deficit of biotinidase leads to low biotin levels, which can cause hair loss skin rashes and brittle nails[23]. rs13078881 (also known as Asp444His or D444H) C allele in the Biotinidase (BTD) gene causes partial biotinidase deficiency[189]. **rs13078881 BTD** polymorphism (**level 1B**) provides an indication to healthcare providers about potential biotin (vitamin B7) deficiency and the need to supplement with biotin and other forms or vitamin B. Biotin supplementation has been shown to be beneficial to hair improvement in cases of inherited biotin deficiency[190]. Topical biotin (see biotin) is often included in hair loss treatment formulas[191-192].

07 CLINICAL VALIDITY REPORT

7.1. Retrospective clinical study

A retrospective case study was performed by the team of the Dr. David Saceda-Corralo (Pedro Jaen Dermatology clinic, University Hospital Ramón y Cajal) using patients with known evolution after treatment. A **Fagron TrichoTest™** analysis was performed for 12 patients with known medical history. Results were analyzed to evaluate the accuracy of **Fagron TrichoTest™** for predicting the treatment responses.

Case 1: **Fagron TrichoTest™** predicted a good response to glucocorticoids without risk of increased plasma levels of angiotensin 2 to a patient with alopecia areata (AA) universalis who was successful treated (>90%) with oral dexamethasone (12 mg weekly) for 6 months.

Case 2: **Fagron TrichoTest™** predicted a good response to glucocorticoids to an AA patient but with a high risk of increased plasma levels of angiotensin 2 (an extremely potent vasoconstrictor associated with hypertension). The patient stopped oral dexamethasone treatment due to adverse effects: arterial hypertension.

Case 3: Case 3 was identical to 2: The treatment was stopped due to arterial hypertension as predicted by **Fagron TrichoTest™**.

Case 4: **Fagron TrichoTest™** predicted a good response to glucocorticoids without the risk of increased plasma levels of angiotensin 2 to an AA patient who was then successfully treated (>90%) with oral dexamethasone (12 mg weekly) for 6 months.

Case 5: **Fagron TrichoTest™** suggested switching to dutasteride and minoxidil to a male patient with androgenetic alopecia (AGA) who was showing a very mild improvement after one year of oral finasteride (1 mg) treatment.

Case 6: **Fagron TrichoTest™** suggested a dutasteride treatment and didn't recommend minoxidil to a male AGA patient who was successfully treated for one year by dutasteride mesotherapy and had a previous unsuccessful treatment with minoxidil.

Case 7: **TrichoTest™** suggested a dutasteride treatment and didn't recommend finasteride to a male AGA patient who was successfully treated for 19 months year with dutasteride after a previous unsuccessful 10-years treatment with finasteride.

Case 8: **Fagron TrichoTest™** suggested a dutasteride treatment and didn't recommend minoxidil (SULT1A1 deficient) to a male AGA patient who was successfully treated for 2 years with oral dutasteride and oral minoxidil. Authors think that the improvement was probably only due to dutasteride.

Case 9: **Fagron TrichoTest™** suggested a dutasteride and minoxidil treatment to a patient with a female pattern hair loss (FPHL) who was showing a moderate response after 12 months of dutasteride treatment (0.5 mg daily).

Case 10: **Fagron TrichoTest™** suggested a dutasteride treatment without minoxidil (SULT1A1 deficient) to a FPHL patient who was successfully treated for 2 years with dutasteride after a previous unsuccessful topical minoxidil treatment.

Case 11: **Fagron TrichoTest™** suggested finasteride to a FPHL patient who was unsuccessfully treated for 24 months with dutasteride, then for 1 year of minoxidil and dutasteride. An improvement was observed after starting a treatment of 5mg finasteride.

Case 12: **Fagron TrichoTest™** suggested a dutasteride treatment without minoxidil to an FPHL patient who was successfully treated for 19 months with dutasteride and had a previous unsuccessful minoxidil treatment.

The test was accurate when selecting or discouraging the use of topical minoxidil and when selecting dutasteride over finasteride. The test also asserted predicting corticosteroid response and suggesting alternative treatment when a risk of hypertension was detected. A parallel survey performed during this study estimated that more than 55% of patients had to change of treatment before noting improvement. Results were presented in the 11th World Congress of Hair Research 2019 and in the 2020 AEDV congress[193-194].

7.2. Post-market surveillance

7.2.1. Risk assessments and PMS data

Fagron TrichoTest™ complies with the essential requirements as set in the Annex I of the Regulation (EU) 2017/746 on in vitro medical devices. Risks assessment shows that the device shows conformity to the intended use during normal conditions of use when weighting known foreseeable risk, against the benefits of the intended use. Post-market surveillance data corresponding to more than 3 years of clinical experience were used for safety assessment.

More than 13.400 patients have been managed by health professionals using our test with a high level of customer satisfaction (4.5/5) and no clinically relevant incident has been reported. The company has processed 2.800 tests in the last 12 months and the projection for 2022 is around 6.000 tests as the company has entered new markets and the test has been launched in June 2021 in the USA by our partner GX sciences (a Fagron's company).

The amount of post-marketing follow-up data is now considerable and indicates that **Fagron TrichoTest™** does not pose an increased risk for the user.

7.2.2. User clinical experience

A user experience of **Fagron TrichoTest™** was recently reported[195] by Dr. Kuka and Dr. Epstein in Hair Transplant Forum International (2021). Dr. Kuka specializes in regenerative medicine for the treatment of alopecia and is the author of numerous papers published in international medical journals. Dr. Jeffrey Epstein is one of the most well-respected hair transplantation surgeons in the world and founder and Director of the Foundation for Hair Restoration and Plastic Surgery.

When reporting their experience, the authors stated:

"*It is our opinion that patients have embraced this concept, something that has been confirmed by Dr. Kuka Epstein's patients, who like the benefit of being provided with a definitive answer as to which treatment has a higher likelihood of being effective for the treatment of their hair loss, sparing the expenses and time waiting for other treatments to work. Patients who have tried different treatments in the past or those who have experienced side effects are particularly motivated to understand better what can work for them.*

Obtaining their genetic profile also makes them more enthusiastic about using a proposed therapy due to a greater confidence in the outcome of the treatment. However, in some cases, even when a genetic profile is defined, the prescribed therapy still might not work:

- *Patients with a more advanced degree of hair loss are less likely to respond to therapy. As with other hair loss therapies, this therapy will show better results in earlier stages of hair loss while follicles are still preserved.*
- *Side effects can result from therapy. In this case report, one patient, apart from not achieving any improvement, developed side effects from a compounding lotion of tretinoin, dutasteride, ginkgo biloba, and SiliciuMax that manifested as headaches and dizziness. Dr. Kuka Epstein then changed this patient to oral dutasteride 0.5 mg five times per week with no side effects noted. It seems like one of the other ingredients named above caused these side effects, despite proven genetic efficacy (1).*
- *While promoted as being indicated for alopecia areata patients, no benefit has been seen in these patients in our practice yet. [...] However, some patients might be responsive to anti-inflammatories (corticosteroids) that are commonly used to treat alopecia areata (2).*
- *One patient who underwent therapy recommended by **Fagron TrichoTest™** showed increased hair loss three months after the therapy. What appeared to be classic androgenic alopecia turned out to be a diffuse alopecia areata (3) that was later confirmed by dermoscopy and biopsy.*
- *For patients with scarring alopecia, it is unclear whether **Fagron TrichoTest™** can be of benefit (4). These conditions have a complex etiology involving auto-immune response of the body where the pilosebaceous unit is destroyed by the scarring process.*

Interestingly, a lot of lotions are dutasteride- rather than finasteride-based, since it blocks all three isozymes of 5-alpha reductase, and mainly in those patients where 5-alpha activity of both isotypes is increased. These patients typically benefit more from dutasteride than finasteride. Around 70 active pharmaceutical ingredients (APIs) can be compounded and are effective in the treatment of hair loss. In-depth research of these APIs provided information on their anti-inflammatory, anti-androgen, or anti-oxidant properties.

Some are used just to improve absorption of the compounding lotion, such as tretinoin or azelaic acid or for that purpose we can opt for a different vehicle to facilitate the delivery of these APIs. There is a major role of vitamins and minerals in hair metabolism, and zinc sulfate is commonly used. The dose of medication varies too. For example, it is rather an exception to have minoxidil 5% suggested, but more often lower doses such as 3% or 4%, which is determined by the level of sulfotransferase activity.

*I find it beneficial to add oral therapy of certain ingredients listed to be used in the lotion. **TrichoTest™** helps not to overtreat, as it will exclude redundant therapy used, for example, the patient who formerly used minoxidil and dutasteride, but the test confirmed highly decreased sulfotransferase activity yet high 5-alpha reductase activity should discontinue the use of minoxidil. This approach minimizes potential side effects of medications that have no effect on the patient's hair loss treatment."*

Fagron Genomics comments

1. This is the first report of a side effect associated to this specific compounding lotions.
2. One of the main benefits of the test regarding alopecia areata is to determine if a patient is likely to be responsive to anti-inflammatory glucocorticoid treatment and to suggest alternative anti-inflammatory treatments if the patient is resistant to glucocorticoids.
3. As AGA was indicated by the prescriber, an AGA treatment was suggested by the algorithm instead of a personalized AA treatment. In this case, the prescriber can request an algorithm recalculation to adapt the treatment to the new diagnostic.
4. Fagron TrichoTest™ is not intended for patients with scarring alopecia.

08 CONCLUSIONS OF THE SCIENTIFIC AND CLINICAL VALIDITY REPORT

Fagron TrichoTest™

is the first genetic test on the market to predict response to alopecia treatments.

Pharmacogenetic test

Fagron TrichoTest™ is a pharmacogenetic test that determines whether a male or female subject having androgenetic alopecia, alopecia areata, or telogen effluvium is likely to be responsive to administration of specific hair loss treatments. A team specialized in genetic variant curation reviewed each variant to ensure that its impact on the algorithms is based on the highest scientific evidence.

Personalizing formulations and dosages

Fagron TrichoTest™ analyses 16 polymorphisms associated with treatment efficacy and combines this information with relevant clinical data to select the most effective and safest active pharmaceutical ingredients. **Fagron TrichoTest™** includes active pharmaceutical ingredients commonly used in clinical practice. Dosages have been prepared by industrial pharmacists and reviewed by dermatologists.

Minimizing the risks of intolerance or contraindications

The patient questionnaire of **Fagron TrichoTest™** has been elaborated by dermatologists and pharmacists to minimize risks of intolerance or contraindications.

Test accuracy

A retrospective case study showed that the test was accurate when selecting or discouraging the use of topical minoxidil, and when selecting dutasteride over finasteride. **Fagron TrichoTest™** also asserted predicting corticosteroid response and suggesting alternative treatment when a risk of hypertension was detected.

Patient satisfaction

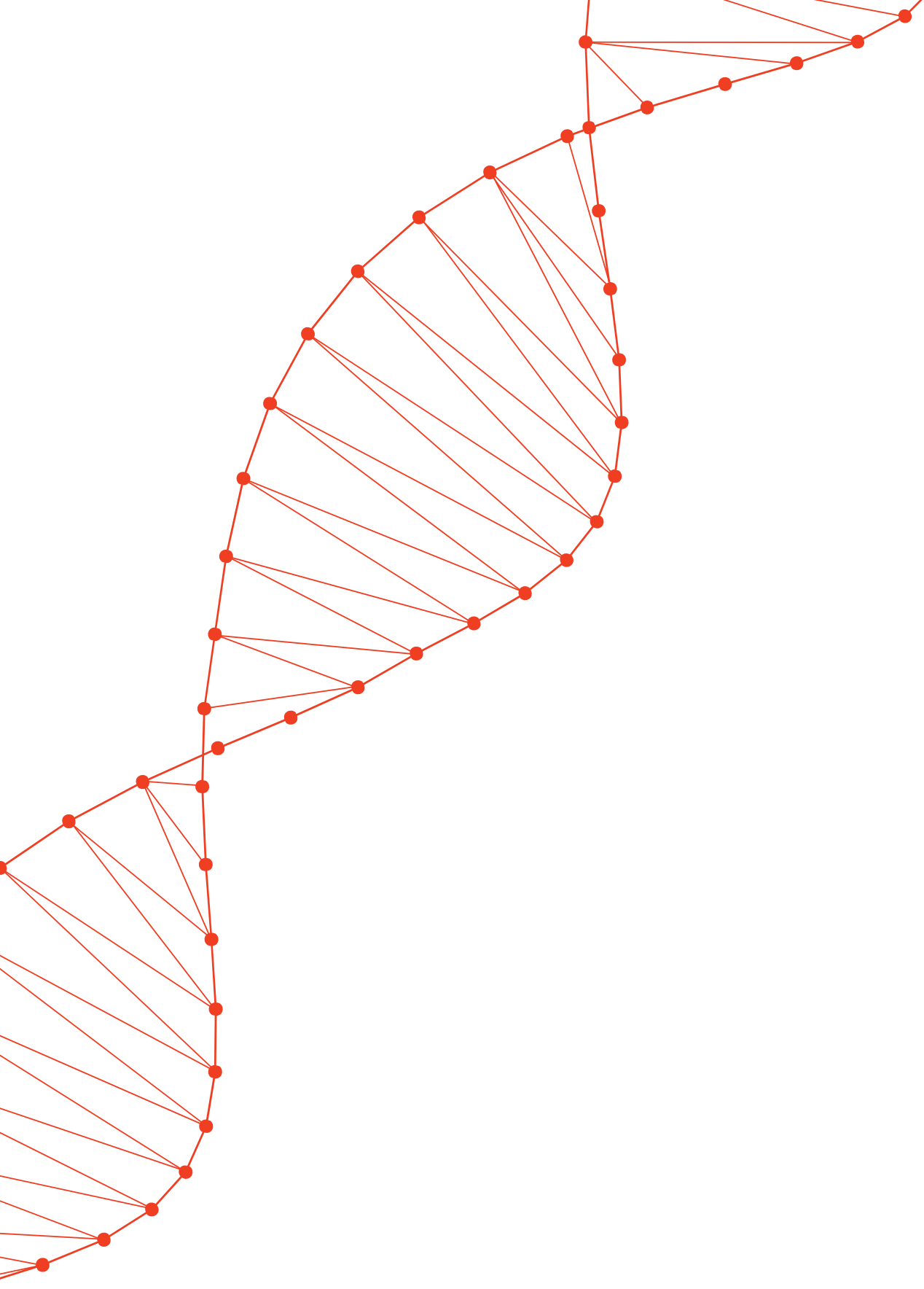
The high degree of customer satisfaction, and the very low level of clinically relevant complaints indicate that the clinical base of **Fagron TrichoTest™** is well-founded, and outputs (genotype descriptions and personalized treatments) well accepted by healthcare professionals and patients.

Saving time and money

Most alopecia treatment should be maintained at least 4- to 6-months before noticing improvement. **Fagron TrichoTest™** saves patients time and money avoiding treatments with a low response rate.

Clinical safety and performance

The analysis of risk management, scientific literature review, clinical experience, and post-market experience with the evaluated device confirms the clinical safety and performance of **Fagron TrichoTest™**. The test shows conformity by achieving the intended performance under normal conditions of use when weighting known or foreseeable risks and adverse events against the benefits of the intended performance.



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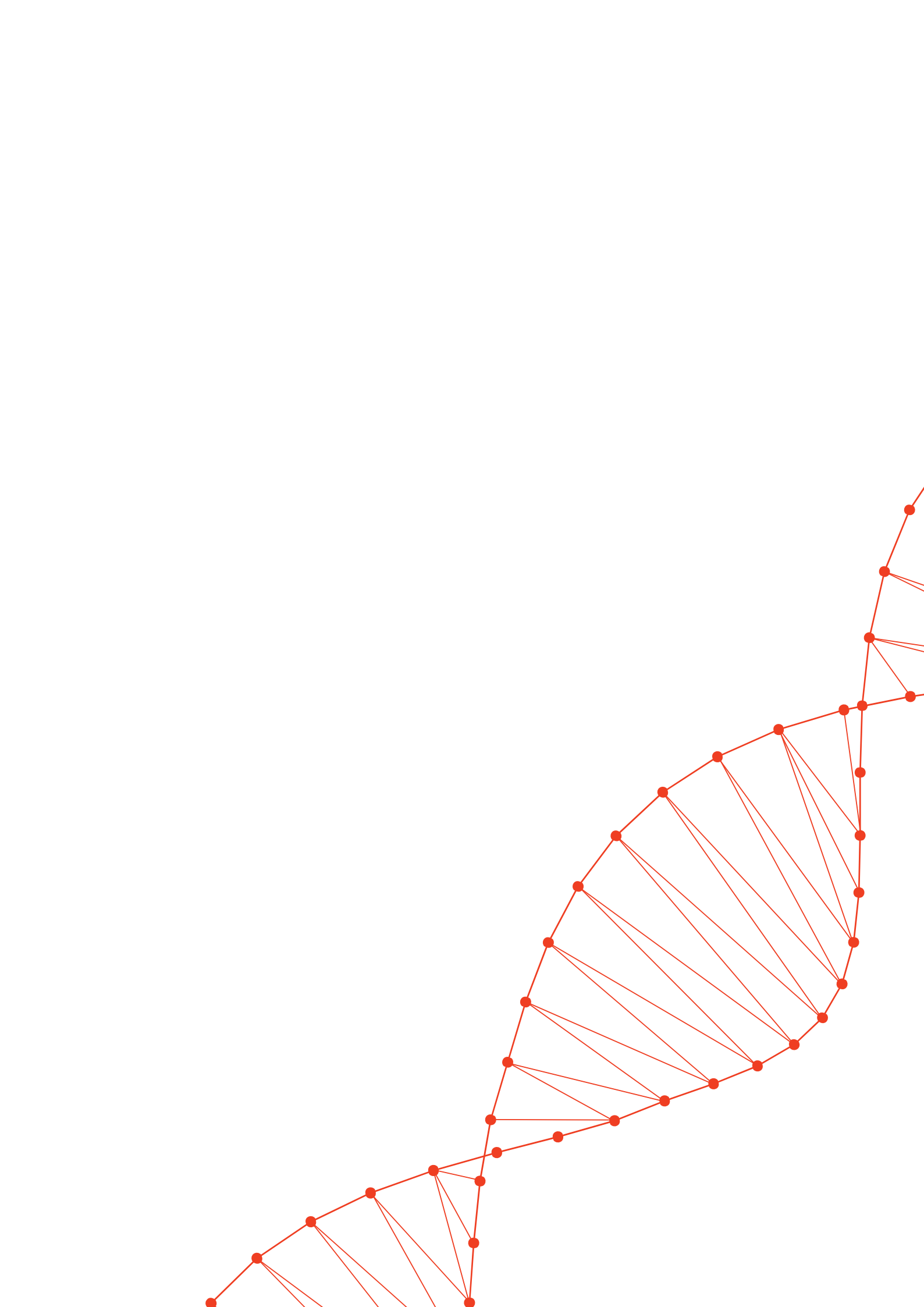

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