Fagron AcneTest

Scientific Dossier

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Fagron genomics

Summary

1. EXECUTIVE SUMMARY

Fagron AcneTest uses an advanced, pharmacogenomics-centered algorithm that assesses skin genetic predisposition and patient anamnesis to guide and improve the treatment of acne.

This test evaluates 60 single nucleotide polymorphisms (SNPs) curated and reviewed by our team of specialists (dermatologists, nutritionists, pharmacists and geneticists). This selection aims to provide relevant clinical information to improve the treatment of acne.

Recommended prescriptions were assembled in accordance with the best clinical practices and international guidelines to ensure that the resulting report significantly improves healthcare outcomes and understanding.

2. INTRODUCTION

2.1 Epidemiology and Relevance

Dermatological skin conditions are a large number of clinical manifestations that can affect between 30% and 70% of the population worldwide[1], and they can vary greatly in symptoms and severity. In the United States, they can affect one in every three Americans, and in 2013, skin diseases were responsible for $ 75 billion in costs to the healthcare system. In Europe, more than 40% of the population has already reported some kind of skin condition[1,2].

Some of these conditions can present more or less impact on the quality of life of different individuals, and their knowledge is of high importance to determine the diagnosis, as well as the adequate treatment, both professional and home care[1]. Acne, rosacea, dermatitis, and hyperpigmentation are among the most common ones, and they can affect the patient simultaneously or as a consequence of each other[1,2].

The different clinical presentations of acne vulgaris are among the eight most common skin pathologies. The estimated Prevalence for the general population is 9.38%, reaching above 90% in specific age groups, i.e., adolescents[3–5]. Despite its Prevalence early in life, acne is also presented in adulthood, beiang specifically crucial in women after 25 years of age[6]. This later is classically referred to as adult female acne[6].

Regardless of the age of onset, a critical remark is that acne might severely impact self-confidence and overall well-being[7]. Furthermore, the inflammation related to the acne lesion might elicit the appearance of scars and hyperpigmentation areas, creating long-lasting consequences, especially if it remains not treated or is poorly treated[8].

Thus, addressing these lesions with adequate therapy is vital for most patients and ensures improvement in quality of life. In addition, relapses are frequent (44% in the general population: 39.9% of ≤20-year-olds vs. 53.3% of >20-year-olds) and often associated with impaired quality of life and a decrease in productivity or even absenteeism[9].

2.2 Acne pathogenesis

The term acne vulgaris, although broad, refers to the inflammation of the pilosebaceous unit, mostly happening in a chronic pattern[10]. Although the pathophysiology of acne is yet to be fully elucidated, the hallmarks of this process are 1) disturbance in the production of sebum, i.e., hyperseborrahoea; 2) altered hormonal regulation in the skin microenvironment; 3) follicular hyperkeratinization; 4) inflammatory response, and 5) altered innate and adaptative response. As a result, the pilosebaceous unit might become impaired, leading to the appearance of comedones. A later and relevant effect is that bacterial growth, mainly of *Cutibacterium acnes*, might increase, eliciting immune response and inflammation, which are features related to the progression of the acne[11].

The initial process is the formation of microcomedones, which evolve into macro (visible to the naked eye) comedones (blackheads or whiteheads). It can develop into inflammatory red papules or pustules – usually on the face, neck, chest, and upper back, where the number of sebaceous follicles is higher (Figure 1). These lesions can then be resolved or develop complications, leading to the emergence of scars, either atrophic or hypertrophic[12].

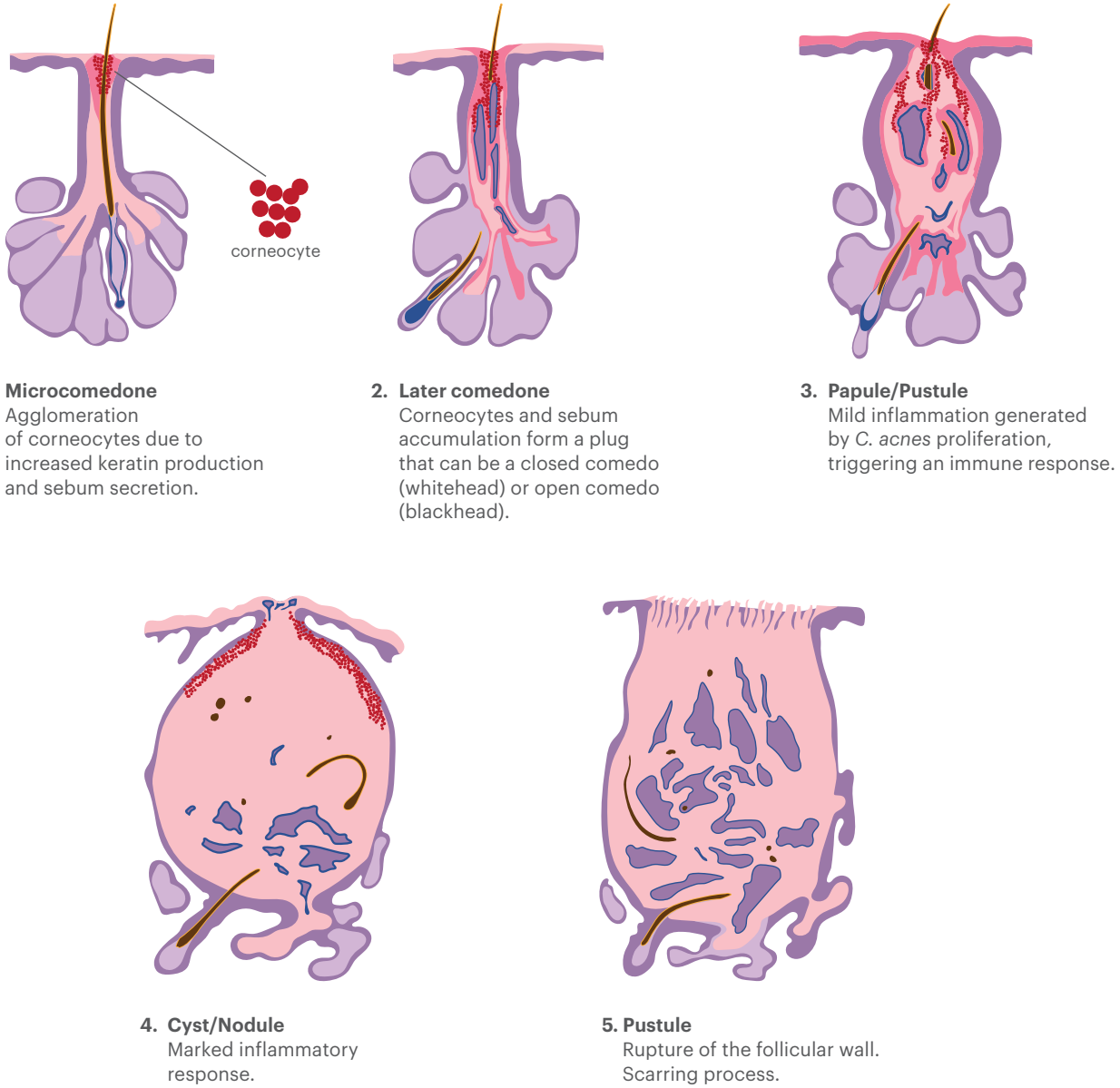


Figure 1. Acne formation process. Adapted[13,14].

Although the onset and development of acne lesions are related to the activity and immunological milieu in the pilosebaceous unit, it is essential to note that both the presence of acne and the severity of the lesions are strongly influenced by genetic factors[15]. Following the initial observation of heredity in acne[16], genetic variations started to be elucidated as risk factors for acne and its grade.

The most recent studies identified several genomic markers as susceptibility loci for acne[17]. Genomic markers for inflammation, cell adhesion, and immune response are generally the strongest correlation, thus indicating those to be relevant biological processes in the pathogenesis of acne[18,19]. The genes and genetic variations employed in the **Fagron AcneTest** will be further discussed and explained in the scientific validity report.

2.2.1 Skin microbiome

The skin microbiome balance is essential because this area is colonized by different microorganisms, such as *Staphylococcus epidermidis* and *Streptococcus pyogenes*. While *S. epidermidis* limits the number of *C. acnes* in the skin, *C. acnes* also limits *S. aureus* and *S. pyogenes*. Thus, dysbiosis can affect the skin barrier and cause inflammation[20,21].

The fungus *Malassezia furfur* is also involved in the process. It can decompose fatty acids and release irritant chemicals to the skin, in addition to the secretion of allergenic proteins and peptides[22]. However, both organisms exist in a commensal relationship in healthy skin. In that case, the intricate microbe-microbiome and microbiome-host interactions are more prone to be a causal factor than the simple colonization by one of these organisms[21].

2.2.2 Receptors in the sebaceous glands

Sebum production is highly implicated in acne pathophysiology. To date, it is known that it can be induced by six receptors expressed in the sebaceous gland (Figure 2): 1) leptin receptor, activated by fat; 2) IGFR-1, activated by sugar; 3) peroxisome proliferator-activated activated by lipids and glucose (PPAR-α, β, and γ); 4) histamine receptors, activated by histamine; 5) hormonal DHT receptor, androgen-sensitive; and 6) neuromodulator receptors, activated by stress-related mediators, e.g., substance P and corticotrophin-releasing hormone (CRH)[20].

The first three are therefore correlated to the diet of the patient. Situations such as peripheral hyperandrogenia (particularly in women) can also abnormally activate the androgen receptors[20].

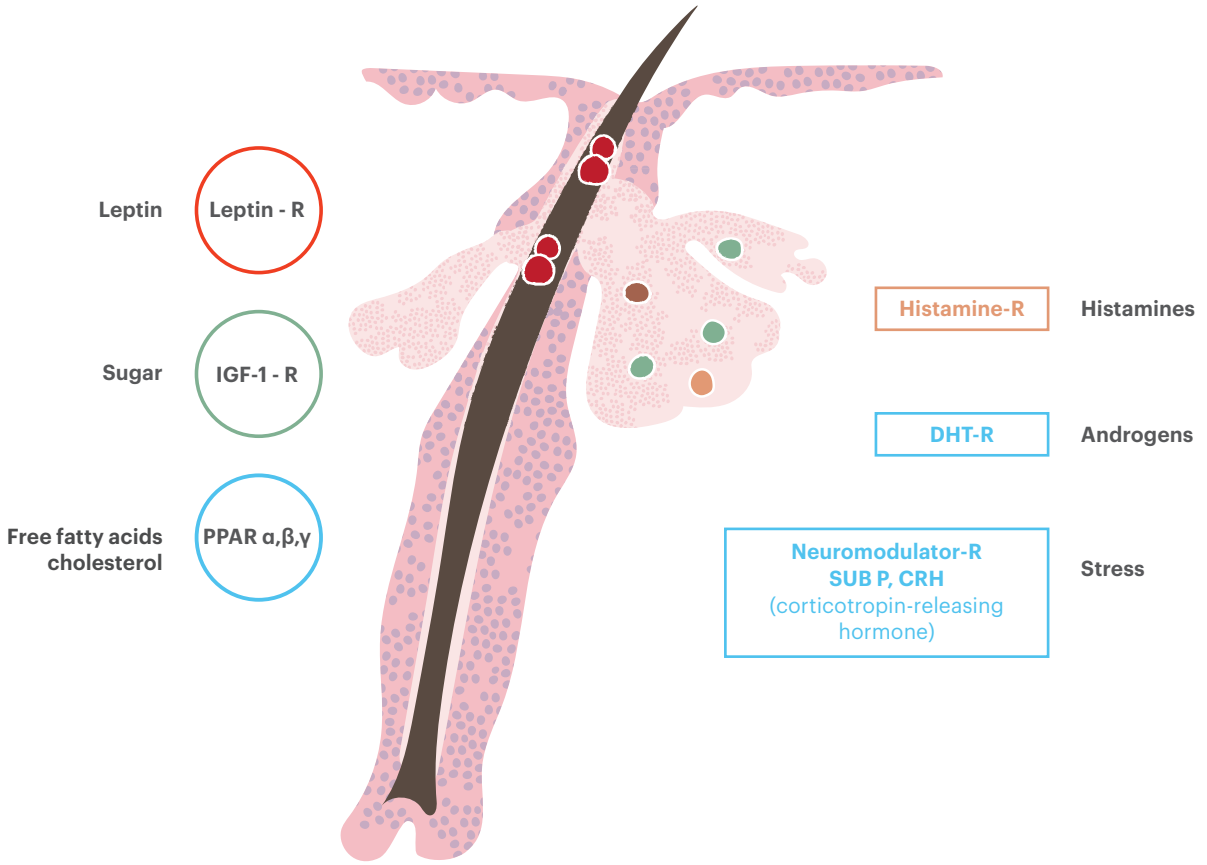


Figure 2. Main receptors involved in sebum production, and their activators. Adapted[20].

2.2.3 Endocannabinoid and immune systems

Another possible player in the development of acne vulgaris is the endocannabinoid system in the skin, which can be involved in different processes, such as differentiation from epidermal appendages (e.g., sebaceous glands). Additionally, it also appears to be involved in sebum secretion control[23].

The immune system can also affect acne emergence (Figure 3). *C. acnes* can promote the release of Th17/Th1-related cytokines, specifically IFN-γ and IL-17A.36 The activation of the innate immunity (via the production of IFN-γ, IL-8, IL-12, TNF-α, IL-1, and MMPs) can result in the hyperkeratinization of the pilosebaceous unit[20,24].

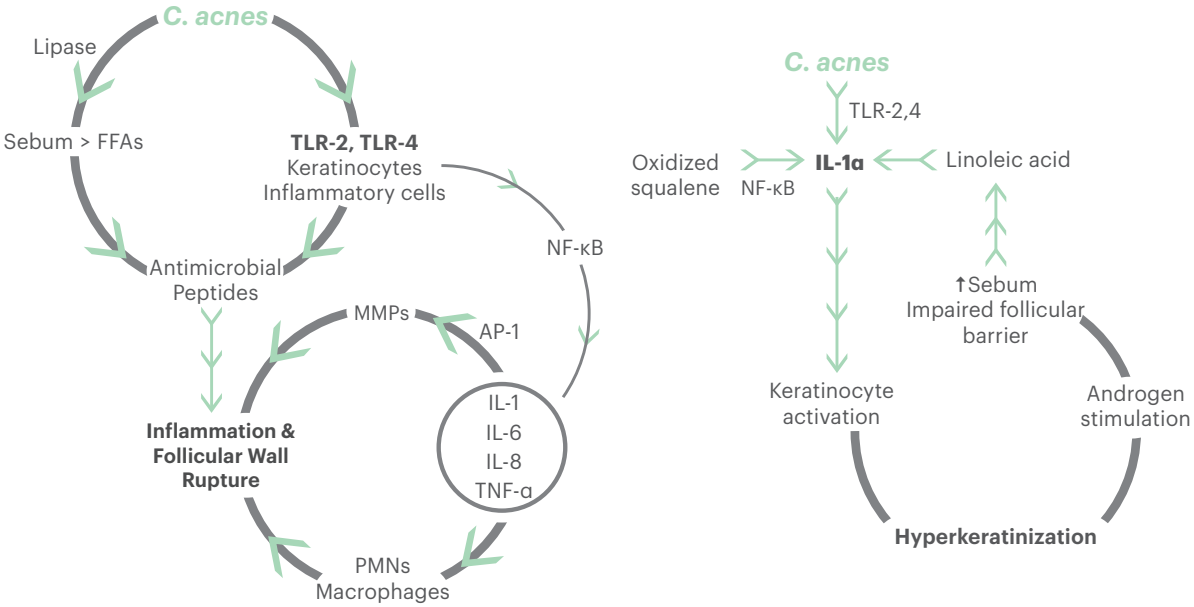


Figure 3. Effect of *C. acnes* in innate immunity and its correlation to acne mechanisms. Adapted [11]. AP: activator protein, FFA: free fatty acid, IL: interleukin, MMP: matrix metalloproteinases, NF: nuclear factor, PMNs: polymorphonuclear leukocytes, TLR: toll-like receptor, TNF: tumor necrosis factor.

2.2.4 Exposome

Finally, the concept of exposome is also being introduced to acne research. Exposome can be understood as the sum of internal and external factors that the person is exposed to from conception until death[25]. In this context, researchers have demonstrated that the main internal factors related to acne are:

- *C. acnes* abnormal proliferation in the skin due to dysbiosis;
- Elevated sebum production;
- Alteration of follicular epithelium (hyperkeratinization due to the hyperseborrhea);
- Inflammatory processes, both in innate and acquired immunities[26].

In addition, the external factors that can play a role in both the severity and treatment efficacy of the disease are:

- **Nutrition (diet)**: mainly dairy products and hyperglycemic carbohydrates;
- **Medication**: hormonal treatments, such as contraceptives, replacement therapies, and anabolic, corticosteroids and immunosuppressants;
- **Occupational factors**: usage of inadequate or aggressive cosmetic products, mechanical stress such as scrubbing and rubbing, affecting the skin microbiome balance, or creating an inflammatory response;
- **Pollutants**: external, such as toxic substances present in the air, or internal, such as tobacco and other drugs exposure, increasing the oxidative damage to the skin;
- **Sun exposure**: ultraviolet radiation triggers inflammatory reactions;
- **Weather factors**: temperature and humidity can trigger the hyperkeratinization of the skin;
- **Psychosocial and lifestyle parameters**: stress, sleep quality, and emotional variations, all inflammatory and oxidative factors[27,28].

2.3 Acne Classification and Sequelae

The course of acne entails an initial non-inflammatory lesion, the comedone that might be followed, depending on several factors, by the onset of inflammation and appearance of papules and pustules, and nodules[10]. The number and presence of the different lesions allow the clinical classification of acne, thus being relevant in determining the initial treatment. The most generally accepted variety of acne is done under the following categories: 1) grade I (comedonal); 2) grade II (papulopustular) ; 3) grade III (nodulocystic); and 4) grade IV (severe nodulocystic or conglobate) [10]. Please refer to figure 4 (also in the **Fagron AcneTest** report for guidance). As previously discussed, the age onset of acne might also yield the diagnosis of acne in the adult woman with distinct underlying features.

Grade V acne refers to the diagnostic of acne fulminans, an emergency-related presentation of the disease that will not be further discussed in this text.

Apart from the traditional grading system, that accompanies the pathogenesis of this condition, the acne in the adult woman needs specific attention and is given a separate classification. As previously mentioned, acne in the adult woman refers to the manifestation of acne in women older than 25 years (check figure 5 for schematic drawing). Although multifactorial, this entity is normally related to hormonal imbalances and alterations in the metabolism of hormones, mainly androgens.

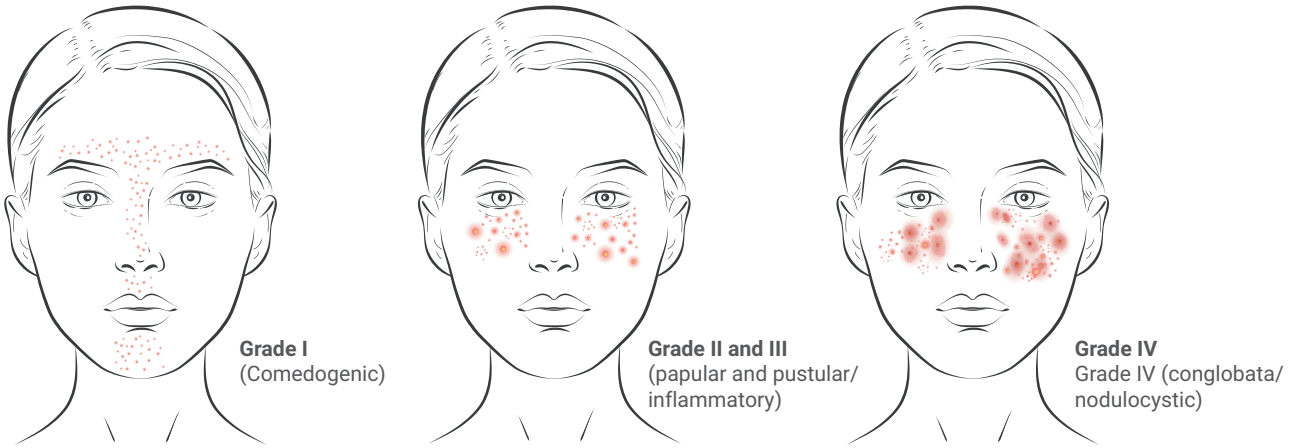


Figure 4. Acne clinical classification: grade I, comedonal; grade II, papulopustular; grade III, nodulocystic; and grade IV, nodulocystic or conglobate.

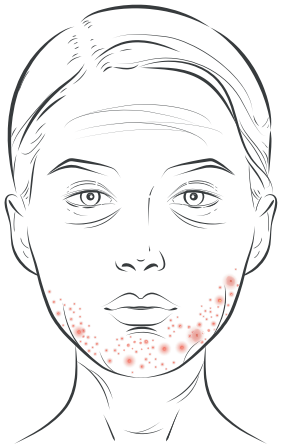


Figure 5. Representation of acne in the adult woman.

The treatment of each grade of acne is started solely due to its clinical presentation, markedly different when the patient presents to the physician with the non-inflammatory and the inflammatory types. The therapeutic recommendations vary from comedolytic and sebolitic topical agents, namely topical retinoids, azelaic acid, and benzoyl peroxide, for grade I acne, to oral retinoids (isotretinoin) for nodular lesions[29]. The pharmacological therapeutic approach to acne is highly variable but generally composed of some core agents, oral and topical antibiotics; retinoids; sebolytics, and antiandrogenic. Due to the characteristic of the lesions and the underlying conditions, the response to the treatment varies considerably. Thus, using several formulations and attempts is expected during the therapeutic course, guided by a clinical approach. It is also important to note that compounding formulations have been proved efficient in personalizing the treatment and finding better solutions[30–32]. Please refer to the review article by Tuchayi et al. (2015) for further references to the primary treatment lines.

Apart from treating acne lesions, the sequelae are often relevant and need specific approaches. Namely, post-inflammatory hyperpigmentation and hypertrophic scars are common patient complaints that need to be addressed[8].

Hyperpigmentation sequelae might be treated with depigmenting agents after their appearance, e.g., hydroquinone, arbutin, azelaic acid, kojic acid, ascorbic acid, and resveratrol[33]. Recent studies have also shown niacinamide to be a potent active ingredient in controlling and reversing hyperpigmentation[34]. However, treating the active acne lesions with retinoids and control of bacterial colonization, thus immune response, has been shown to improve outcomes and mitigate the formation of hyperpigmentation and hypertrophic scars[8]. Therefore, initiating proper and early treatment is relevant in reducing the chances of long-lasting consequences[35,36].

There is also evidence that acne can impact the difficulties in emotion regulation (DER) scale, notably in the form of anxiety and depression[37]. This occurs because acne lesions can become scarring, affecting psychological factors.

Acne scars can be divided into three main groups: ice pick scars, rolling scars, and boxcar scars, as well as some less common lesions such as sinus tracts, hypertrophic scars, and keloidal scars (Figure 6)[38].

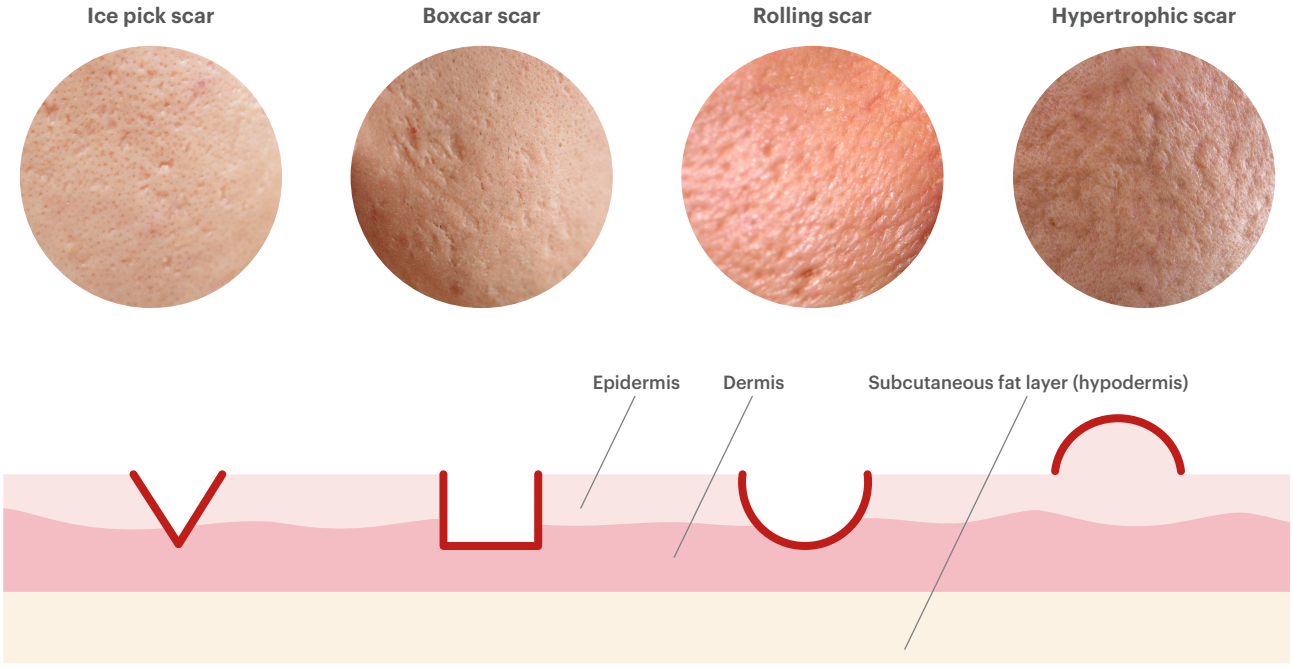


Figure 6. Examples of the different types of scars that can be resulted from acne lesions. Adapted[38].

Inflammation is one of the hallmarks of the development of acne and its potential long-lasting consequences. Therefore, it is expected that genetic variations related to increased levels of mediators found during inflammation are also associated with the predisposition to displaying post-inflammatory hyperpigmentation and hypertrophic scars.

This stresses that genotyping patients for those variations might aid in guiding acne treatment. Notably, the polygenic risk score measurements correlate better statistically to severe acne, indicating the possibility of better predicting this condition for cases requiring more specific treatment[18].

3. UNMET MEDICAL NEEDS

Although widely known, the standard pharmacological treatment of acne may depend on many factors to succeed. Furthermore, relapses might occur, significantly worsening the life quality of patients[9,39]. Besides, side effects of the common treatments might be relevant. Skin sensitivity to topical treatments and liver and lipidemia alterations when using isotretinoin are commonly found side effects. These side effects might hinder or delay the progress of the treatment course. Despite being the most employed treatment, meta-analyses have shown isotretinoin to be efficient in clearing 32% to 69% of the lesions[40]. Although consistently superior to placebo, no treatment offers definitive treatment for acne.

Considering that, providing further information regarding the predisposition to severe acne and altered immune response pattern allows for better deciding the initial treatment. Furthermore, understanding the genetic propensity to adverse effects will guide dermatologists in mitigating potential harmful consequences of treatment.

Furthermore, it was noted that the greater the severity of acne, the more influence genetic factors exert[18]. The presence of genetic markers of risk for severe acne is used in the **Fagron AcneTest** as indicators to begin treatment with oral antibiotics and retinoids.

There is currently no test comparable to the Fagron AcneTest in the market

Acne treatment entails using topical and oral agents depending on the grade diagnosed. However, no genetic test for predicting predisposition to acne and treatment response has been developed.

The Fagron AcneTest fills unmet medical needs

Acne grading and several other clinical factors that influence treatment are considered through a comprehensive questionnaire.

The **Fagron AcneTest** offers a complex algorithm that combines genetic data from 60 SNPs with relevant patient history collected through questionnaire. It provides comprehensive genetic data related to acne susceptibility and treatment and personalized formulations based on 73 possible active pharmaceutical ingredients (APIs).

There is currently no test comparable to the **Fagron AcneTest** 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 of the report are displayed in a comprehensible fashion so that they are self-explanatory.

The company also organizes training sessions training for non-geneticist health care providers and provides 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.

4. INTENDED USE

Fagron AcneTest is intended to assist health professionals in making patient-specific care decisions regarding the treatment of acne and the prevention of sequalae that might appear as later consequences. It analyses 60 single nucleotide polymorphisms associated with metabolic pathways and biochemical mechanisms involved in the development of acne and its consequences as well as in the response to treatment. It combines this information with relevant patient anamnesis to recommend the most appropriate treatment and to provide relevant clinical-genetic correlation. Genetic data are obtained from commercially validated biomedical assays performed on DNA extracted from buccal swab.

5. METHODOLOGY APPLIED FOR THE DEVELOPMENT OF THE TEST

Fagron AcneTest was developed by a multidisciplinary team of dermatologists, 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 that can affect algorithm outputs (recommended products, formulation) was taken into account through medical questionnaires elaborated by dermatologists. 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, e.g. companion diagnostics, are *in vitro* diagnostic medical devices. Applicable standards and relevant guidance documents for **Fagron AcneTest** 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.

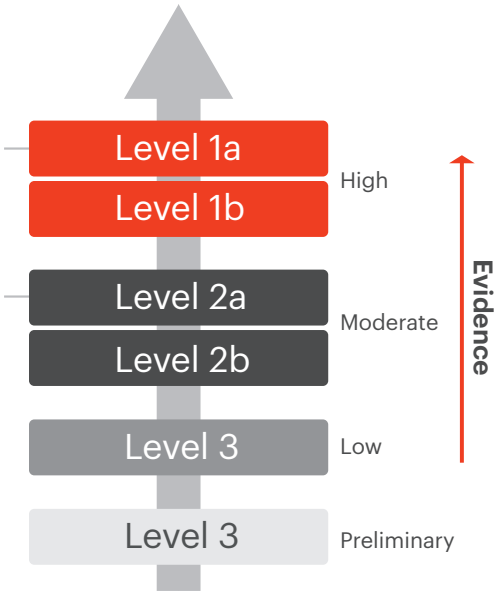
5.2 Methodology applied for justified rating & selection of literature

The following methodology was used for an objective and justified rating & selection of literature for **Fagron**

AcneTest *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 as- say evidence only.



6. SCIENTIFIC VALIDITY REPORT

The **Fagron AcneTest** is a pharmacogenetic test that allows for better treatment and offers a comprehensive understanding of the patient's immune response and predisposition to several processes related to acne pathophysiology and treatment. The **Fagron AcneTest** report is organized into the following macro-categories that will be further explained below: I) skin predisposition to acne; II) skin condition and inflammation; III) predisposition to hormone-related acne; IV) nutritional advice; V) pharmacogenetics.

I. Skin Predisposition to Acne

Although a multifactorial disease, the pathogenesis of acne usually entails disbalances in the production of sebum, keratinization, and altered immune response to the presence of microorganisms in the microenvironment[10]. Therefore, it is expected that genomic markers of inflammation and skin metabolism predict the predisposition to acne and the severity of its presentation. Please find in Table 1, the SNPs employed by the **Fagron AcneTest** to assess this factor.

Gene Related	SNP	Gene Function	Pathogenic alteration due to Polymorphism	Reference
IL-1B	rs16944	Interleukin involved at the beginning of inflammation	Increased secretion of IL-1B, which is correlated to the pathogenesis of inflammation and acne	41, 42
FST	rs38055	Regulates function and levels of TGF-β, being involved in inflammation and sebum control	Impaired control of TGF-β- related inflammation and augmented sebum production	17
TGF-β2	rs1159268	Cytokine is related to inflammation and cell proliferation during an immune response	Increased levels of TGF- β2 and exacerbated inflammation leading to a predisposition to acne	17
OVOL1	rs478304	Transcription factor that regulates differentiation of keratinocytes	Hyperproliferation of keratinocytes, leading to altered sebaceous gland function	17
TLR4	rs4986790 rs4986791	Receptor for recognition of pathogen patterns in the innate immunity	Altered activation of the innate immunity against *Cutibacterium acnes* mainly leads to the risk of *acne conglobata*	41, 43
MYC	rs4133274	Cell growth control and androgen receptor expression control	Altered cell growth and dysregulation of sebum production, leading to increased severity of acne in teenagers	41, 44
CYP17A1	rs743572	Steroid 17-alpha-monooxygenase	Altered hormone balance, leading to increased sebum production and acne severity	41

Table 1. Summarized SNP information related to Skin Predisposition to Acne.

II. Skin Condition and Inflammation

As well as early inflammation and immune response markers being involved in the pathogenesis of acne, they also correlate to the biological processes associated with the appearance of acne-related sequelae, e.g., post-inflammatory hyperpigmentation and scars. Furthermore, immune-mediated skin sensitivity might also impose problems when prescribing topical agents for acne treatment. In Table 2, we have summarized the SNPs studied in the **Fagron AcneTest** to evaluate the risk of sequelae and other skin conditions relevant to the treatment.

It is noteworthy that, besides other mechanisms, melanocytes respond to cytokines and other mediators that are typically secreted during inflammation.

Gene Related	SNP	Gene Function	Pathogenic alteration due to Polymorphism	Reference
MYEF2	rs1426654	Myelin expression factor influences the expression of several genes, including the control of pigmentation	Altered production of melanin increases the predisposition to hyperpigmentation	45
TNF-α	rs1800629	Cytokine that binds to its receptor activating the function of the NF-κβ, and MAPK pathways, eliciting inflammation	Higher levels of TNF-α lead to more severe inflammation and induce the production of more pigmentation by the melanocytes	41
IL-10	rs1800896	Interleukin typically involved in the control and end of immune response	Decreased secretion of IL-10, which might impair inflammation control leading to post-inflammatory hyperpigmentation	46,47
PIK3R1	rs10515088	Control of the phosphoinositide 3-kinase pathway that is implicated during cell proliferation and also immune response	Indication of altered sebum production and possible increased risk of acne	48
HLA-DRA	rs763035	Determines the expression of the isotype DR of the HLA	Altered expression of the HLA-DRA determines predisposition to rosacea	49
FLG	rs7927894	Filaggrin gene, a protein associated with a filament protein that binds to keratin fibers in epithelial cell	Increases skin sensitivity	50
IRF4	rs12203592	Interferon Regulatory Factor 4 determines the expression of interferon and, thus, inflammation	Determines augmented skin sensitivity	51
MTA3	rs17030203	Nuclear receptor that determines the expression of several genes	Altered levels of the MTA3 protein and proteins regulated by it lead to increased skin sensitivity	52
WNT10A	rs74333950	Protein is related to one of the WNT pathways that regulate cell proliferation	Increased risk of acne, hyperpigmentation, and scars	18

Gene Related	SNP	Gene Function	Pathogenic alteration due to Polymorphism	Reference
LncRNA	rs873549	Long non-coding RNA altering the expression of several genes	Increases the risk of keloid formation	53,54
FOXL2	rs1511412	Transcription factors altering the expression of several genes	Increases the risk of keloid formation in asians	53,55
RETN	rs3745367	Resistin is a secretory factor related to the adipose tissue, determining the circulation of lipids and inflammation control	Related to acne relapse	56
	rs1862513			

Table 2. Summarized SNP information related to Skin Condition and Inflammation.

A thorough understanding of the susceptibility to acne sequelae enables rapid action in recommending agents that control and treat hyperpigmentation and inflammation associated with scarring.

III. Predisposition to Hormone-related Acne

Acne is most commonly described as presenting its onset during adolescence; however, hormonal factors might be predominant in the pathogenesis of acne in women, whose lesions might begin or continue until adulthood. In Table 3 below, we have summarized SNPs related to hormonal alterations that might predispose to altered testosterone metabolism and, thus, acne. Furthermore, polycystic ovary syndrome is a general pathology for which acne is a meaningful clinical sign. Therefore, understanding that the patient is predisposed to these alterations should direct the healthcare professional's attention to this line of thought. Given the possibility of hormone-related alterations leading to acne, medical professionals may recommend the use of antiandrogens to treat acne.

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Gene Related	SNP	Gene Function	Pathogenic alteration due to Polymorphism	Reference
CYP17A1	rs743572	Steroid 17-alpha-monooxygenase	Altered hormone balance, leading to increased sebum production and acne severity	41
MYEF2	rs1426654	Myelin expression factor influences the expression of several genes, including the control of pigmentation	Altered production of melanin, with potential to increase the risk of hyperpigmentation	45,57
CYP19A	rs700518	The aromatase enzyme converts androgen hormone (e.g., testosterone) into estrogens, thus controlling the influence of androgen hormones	Altered aromatase function, leading to increased testosterone levels. Might be related to increased sebum secretion.	58,59

Gene Related	SNP	Gene Function	Pathogenic alteration due to Polymorphism	Reference
THADA	rs13429458 rs12478601	Regulates calcium signaling	Increased risk of polycystic ovary syndrome	60 - 63
LHCGR	rs13405728	Receptor for the luteinizing and choriogonadotropin hormones, regulating ovary function	Increased severity of symptoms of polycystic ovary syndrome	60,63
FSHR	rs2268361 rs2349415	Receptor for the follicle-stimulating hormone receptor, determining response to it by the ovaries	Increased risk of polycystic ovary syndrome	60,62, 64

Table 3. Summarized SNP information related to the Predisposition of Hormone-related Acne.

IV. Nutritional Advice

The nutritional and metabolic states of the patient also exert a significant influence on the functioning of the sebaceous gland. Specifically, dietary lipids and glycemia modulate critical pathways that directly increase sebum production. The nutritional lipids and glucose induce hyperseborrahoea through the activation of PPAR pathways. Furthermore, lipidaemia also modulates more general inflammation mechanisms[10].

The use of isotretinoin, also known as 13-cis-retinoic acid, impacts glucose and lipids' metabolism with hyperlipidemia as a possible side effect. Variations in the retinoid receptor have been shown to increase the risk of having an alteration of lipid levels. Thus nutritional advice would be essential for those patients. Table 4 below indicates the SNPs and their consequences to consider when approaching a patient from a nutritional point of view.

Gene Related	SNP	Gene Function	Pathogenic alteration due to Polymorphism	Reference
RXR	rs283696 rs10918169 rs2651860 rs1128977	Retinoid receptors; regulate the expression of several genes	Increased risk of familial hyperlipidemia	65,66
SOAT1	rs404818	The sterol O-acyltransferase involved in the synthesis of cholesterol esters	Increased lipidemia and risk of atherosclerosis	18
PNPLA3	rs738409	This enzyme functions as a triacylglycerol lipase in adipocytes, releasing fatty acids	Increased risk of acne, increased lipidemia, and risk of hepatic steatosis	18

Gene Related	SNP	Gene Function	Pathogenic alteration due to Polymorphism	Reference
TM6SF2	rs58542926	Transmembrane protein is involved in the triglyceride secretion and hepatic lipid droplet content regulation	Increased LDL and insulin levels	67
APOE	rs4420638	Apolipoprotein is found in chylomicron remnants, VLDL, LDL, regulating the circulation and uptake of lipoproteins	Increased levels of LDL	67
ABCG8	rs6544713	Involved in the transport and secretion of synthesized cholesterol	Increased LDL levels	68
HN-F1A-AS1	rs2650000	Regulates proliferation and cell function in hepatocytes	Increased LDL levels	68
GHRL	rs27647	Ghrelin And Obestatin Prepropeptide, thus, involved in the secretion of ghrelin and appetite regulation	Altered satiety response	69,70
FLG-AS1	rs12123821	Antigen uptake, processing, and immune response	Increased risk of food allergy	71,72
IL-13	rs1295686			
C11orf30/ LRRC32	rs2212434			
SERPINB7	rs12964116			
FTO	rs8050136	Regulates DNA methylation and gene expression of several genes	Increased risk of obesity and impaired glucose level control	
ODZ4	rs7103693	Transmembrane protein that translocates to the nucleus and regulates cell proliferation, activity, and adhesion.	Altered decrease in fasting glucose levels	73
ARAP1	rs9667947	Regulates several cellular control mechanisms	Increased glucose levels and risk of DM2	74
FABP2	rs1799883	Involved in the transport and uptake of long-chain fatty acids	Increased sensitivity to refined carbohydrates	74

Table 4. Summarized SNP information related to the Nutritional Advice.

Although the nutritional approach is not defined as first-line therapy for acne, the possibility of understanding patient predisposition to metabolic alteration allows interfering with pathways that increase the risk of acne.

V. Pharmacogenetics

Pharmacogenetics analyzes the genetic variants that might impact the response to drugs. Response to drugs might vary due to alterations in enzymes involved in the metabolism and drug concentration, i.e., pharmacokinetic processes, and in the very molecular mechanism of the drug, namely pharmacodynamic.

The drugs employed in the treatment of acne often need necessary drug adjustment. In table 5, we have outlined the polymorphisms used in the **Fagron AcneTest** to evaluate the patient's pharmacogenetic profile regarding the essential active ingredients used to treat acne.

Gene Related	SNP	Gene Function	Pathogenic alteration due to Polymorphism	Reference
RXR	rs283696 rs10918169 rs2651860	Retinoid receptors; regulate the expression of several genes	Increased risk of familial hyperlipidemia related to retinoid receptor	65
CYP3A5	rs776746	Drug metabolism	Higher activity of the CYP3A5 enzyme was shown, generating faster clearance of drugs metabolised by CYP3A5, retinoids are potentially affected by this alteration	75
CYP3A4*22	rs35599367	Drug metabolism	Slower metabolism of erythromycin related to lower enzyme activity of CYP3A4.	76
CYP3A4*2	rs2737418	Drug metabolism	Slower metabolism of erythromycin related to lower enzyme activity of CYP3A4.	76
CYP3A4*11	rs28988604	Drug metabolism	Lower activity of the CYP3A4 enzyme was shown, generating slower clearance of drugs metabolised by CYP3A4, erythromycin, clindamycin, cyproterone, and dapsone are potentially affected by this alteration	76,77
CYP3A4*20	rs67666821	Drug metabolism	Lower activity of the CYP3A4 enzyme was shown, generating slower clearance of drugs metabolised by CYP3A4, erythromycin, and cyproterone are potentially affected by this alteration	76,78,79
OATP1B1	rs4149056	Drug transport	Lower activity of the OATP1B1, reducing transport of several drugs. Erythromycin pharmacokinetics might be affected	80,81
ABCC2	rs717620	Drug transport	Higher activity of the ABCC2 enzyme, as it is know to be involved in the metabolism of erythromycin, it might reduce its serum concentration	82
HLA-DRB1	rs701829	Antigen presentation	Hypersensitivity to dapsone in Asians	83
HLA-B*13:01	rs2844573	Antigen presentation	Hypersensitivity to dapsone in Asians	84

Gene Related	SNP	Gene Function	Pathogenic alteration due to Polymorphism	Reference
CYP2C9*2	rs1799853	Involved in drug metabolism	Lower activity of the CYP2C9 enzyme was shown, generating slower clearance of drugs metabolised by CYP2C9, dapsone is potentially affected by this alteration	85
CYP2C9*3	rs1057910			85
CYP2C9*5	rs28371686			85
CYP2C9*8	rs7900194		Higher activity of the CYP2C9 enzyme was shown, generating faster clearance of drugs metabolised by CYP2C9, dapsone is potentially affected by this alteration	85
HLA-B*51:01	rs2442736	Antigen presentation	Hypersensitivity to clindamycin	86

Table 5. Pharmacogenetic targets employed in the **Fagron AcneTest**.

7. CONCLUSIONS

The **Fagron AcneTest** is the first genetic test on the market to predict acne treatment and skin features related to acne and its sequelae. The test analyses 60 polymorphisms associated with predisposition to acne and severity of its presentation; scars and post-inflammatory hyperpigmentation; hormonal imbalances leading to acne; and metabolic parameters related to acne pathogenesis. Furthermore, we evaluate pharmacogenetic parameters regarding metabolism and response to the primary drugs used for acne therapy. The **Fagron AcneTest** offers the possibility to personalize the acne treatment by providing information regarding the patient's genetic information related to several acne pathological processes.

The test report relies on genetic variants associated with the individual propensity to acne and its sequelae. Additionally, a clinical questionnaire developed and validated by world-renowned dermatologists considers anamnesis data in deciding the ideal medication for each patient.

Fagron AcneTest includes active pharmaceutical ingredients commonly used in clinical practice to treat cases of each grade of acne. Formulations and dosages suggested by the algorithm were prepared by industrial pharmacists and reviewed by dermatologists.

The accuracy of **Fagron AcneTest** relies on the consistency of the association between genetic variants and predisposition to a medical condition o treatment response. Genetic variants have been methodically selected and appraised. Their association to a clinical condition, physiological state and genotype interpretation have been carefully reviewed. The scientific literature supporting the treatment options and the patient questionnaire have been reviewed by doctors, nutritionists and pharmacists in order to maximize the response to treatment and minimize the risks of intolerance or contraindications.

In conclusion, the design of this genetic test takes into consideration an in-depth literature review and clinical practice to generate recommended prescriptions that considerably improve the treatment of acne.

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Fagron Genomics, S.L.U carries out genetic tests upon request by healthcare professionals, in relation to biological samples from patients obtained by the healthcare professional. Our tests do not replace a medical consultation, nor do they make up a diagnostic or treatment, nor should they be interpreted this way. Only healthcare professionals can interpret the results of said tests, based on their knowledge of the clinical records of the patients and other relevant factors and, under their responsibility, give a diagnosis or prescribe treatment to the patient. We decline all responsibility derived from the use and interpretation of the results of our tests by the requesting healthcare professional.

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