Fagron TeloTest

Scientific base of a Telomere test algorithm for the prevention of aging

Fagron genomics

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Summary

1. EXECUTIVE SUMMARY

Fagron TeloTest is intended to assist health professionals in making patient-specific care decisions regarding the prevention of cellular aging, especially in high yield diagnostic settings, such as suspected cases of short telomere syndromes, genetic variation in telomere genes, and in the evaluation of bone marrow failure and related disorders.

Unlike its competitors, **Fagron TeloTest** is offered exclusively to practitioners that can value its usefulness in specific conditions like illness that runs in families. Besides providing information about potential premature shortening, results from a telomere length test can be motivating for individuals who wish to adopt healthier lifestyles.

The practitioner logs into Fagron's digital health platform, enters the patient's data, and completes the corresponding medical questionnaire. This questionnaire contributes to the individualized assessment of the patient, considering possible contraindications and allowing the personalization of supplementation and health advice.

Following the instructions provided in the sampling kit, the practitioner collects the buccal swab sample and sends the sample for analysis to our clinical laboratory. The sample is analyzed using a standardized Real-Time Quantitative PCR method for measuring telomere length. Telomeres tend to shorten with age or with epigenetic age acceleration.

Fagron TeloTest algorithm analyses quantitative data, calculates telomere length, infers biological age based on telomere length, and interprets results and relevant patient's anamnesis to recommend the most appropriate formulas and advice to delay the effect of cellular aging.

The following dossier, intended for prescribers, aims to deepen their understanding of **Fagron TeloTest** for optimal patient support. After an overview of telomere attrition as a biomarker of cellular aging, this dossier describes the scientific basis of the test.

2. INTRODUCTION

The growing elderly population in European countries, accompanied by the increasing prevalence of chronic diseases associated with aging, will have profound implications for the health care system for decades to come. Major challenges will be how to prevent age-related diseases and how to encourage a healthy lifespan in large and increasing populations of elderly individuals. Numerous studies have demonstrated the effects of active pharmaceutical ingredients and nutraceuticals in reducing oxidative damage and promoting healthy aging and the benefits of lifestyle interventions. Identifying and exploiting reliable biomarkers of aging is a major goal in geroscience.

Clinicians currently use a plethora of variably effective biomarkers to define the aging characteristics of patients: age, serum metabolite levels, physiological measures, and functional tests. Telomere attrition is a natural phenomenon widely recognized as one of the hallmarks of aging and useful indicator for assessing the overall aging process in human patients[1-2].

The telomere length theory of ageing was recognized by the Nobel Prize in Medicine/Physiology in 2009. The difference between the epigenetic clock and the chronological age is being termed epigenetic age acceleration[3], which has been shown to be associated with mortality independently of the chronological age[4]. Telomerase, a telomere-lengthening enzyme, helps to maintain the telomere 3´ overhang and thus the integrity of the chromosome. Telomeres shorten during each cell division in the absence of telomere synthesis mechanisms such as telomerase. When telomeres reach a critically shortened length, chromosomal aberrations such as end-to-end fusion occur, and cells enter senescence or undergo apoptosis and are no longer able to replicate. Several systematic reviews have investigated the associations between accelerated telomere shortening and age-related disease[5] and telomere shortening is identified as a key biomarker for accelerated aging, disease risk, and longevity.

3. UNMET MEDICAL NEEDS

Telomere shortening is identified as a very informative marker in accessing the biological age when used along with complementary information like individual assessment or other markers. **Fagron TeloTest** uses an automatized qualitative algorithm that calculate telomere length, infer biological age based on telomere length and recommends the most appropriate formula and lifestyle and nutrition recommendations to delay the effect of ageing in male and female population.

Tests like **Fagron TeloTest** exist in the market (Teloyears, Spectracell telomere, Life Length, etc.) based on the same technology; however, they do not include health-related data to personalize supplementation and health advice. Other important difference is that competitors' products are direct-to-consumer tests while the **Fagron TeloTest** service is offered to practitioner that can value its usefulness in specific conditions like illness that runs in families. Telomere length testing is most informative in high yield diagnostic settings, such as suspected cases of short telomere syndromes, genetic variation in telomere genes, and in the evaluation of bone marrow failure and related disorders. **Fagron TeloTest** questionnaire contributes to patient's individualized assessment and allows the personalization of supplementation and health advice. To our knowledge, no similar device exists in the market.

The module is accessible through Fagron Genomics Medical Software, an online medical platform intended to be used exclusively by healthcare professionals (intended users) with the purpose of helping them in managing their patient's genetic tests. The 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 the practician's work, the test results of the report are displayed in a comprehensible fashion so that they are self-explanatory. The company also provides **training sessions** for non-geneticist health care providers and a support line 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.

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.

4. INTENDED USE

Fagron TeloTest is intended to assist health professionals in making patient-specific care decisions regarding the prevention of cellular aging, especially in high yield diagnostic settings, such as suspected cases of short telomere syndromes, genetic variation in telomere genes, and in the evaluation of bone marrow failure and related disorders.

Fagron TeloTest analyses quantitative data associated with the length of telomeres that tend to shorten with age. Quantitative data are obtained from a specific laboratory telomere length assay performed on DNA extracted from buccal swab. Fagron TeloTest uses an automatized qualitative algorithm that calculates telomere length, infer biological age based on telomere length, and interprets results and relevant patient's anamnesis to recommend the most appropriate formulas and advice to delay the effect of cellular aging in adult male and female population.

5. METHODOLOGY APPLIED FOR THE DEVELOPMENT OF THE TEST

Fagron TeloTest was developed by a multidisciplinary team of research scientists, medical doctors, nutritionists, pharmacists, and programmers, following highest quality standards. In particular, an expert team specialized in the examination of scientific publications reviewed each claim 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 (advice and supplements) was taken into account through medical questionnaires elaborated by health professionals. The most authoritative resources on active pharmaceutical ingredients, dietary supplements, food compositions, 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 TeloTest** 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 TeloTest** *in vitro* diagnostics 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.

6. SCIENTIFIC VALIDITY REPORT

6.1 Telomere shortening as a key biomarker for accelerated aging

In the past 10 years, several systematic reviews have investigated the associations between accelerated telomere shortening and age-related disease[5] and telomere shortening is identified as a key biomarker for accelerated aging, disease risk, and longevity. Telomeres are protective caps on the ends of the chromosomes that protect them from deterioration or fusion to other chromosomes during cell-division. As a cells ages, its telomeres become shorter and the speed of telomere shortening may indicate the pace of cellular aging. Telomere length, shorter than the average telomere length for a specific age group, may be related with early onset of many age-associated health problems, including coronary heart disease, diabetes, increased cancer risk, and osteoporosis[5].

The clinical value of telomeres can be demonstrated in its importance in cancer, premature aging syndrome or segmental progeria, genetic anomalies, and age-related diseases[6-8]. Numerous studies suggest that telomere length is influenced by a variety of social-environmental, psychosocial and lifestyle factors[5] and is potentially modifiable. Lifestyle changes (improved nutrition, stress management, moderate exercise, and support session) significantly increase telomerase activity and consequently telomere maintenance capacity[9-10].

Multiple methods have been developed to measure telomere length. These techniques include quantification of telomere length by terminal restriction fragmentation which was one of the earliest tools used for length assessment making it the gold standard in telomere biology. However, nowadays the Real Time Quantitative PCR (RT-qPCR) method for measuring telomere length[11] has been widely adopted due to its relatively easy and quick application, lower cost, and smaller DNA quantity requirement (60 ng/sample) compared to the traditional terminal restriction fragmentation analysis (0.5–5 g/sample). Relative quantification is based on the expression levels of a target sequence and a reference gene. In case of telomere length measurements, the target sequence is telomere and a single copy gene is used as the reference gene. The ratio of the telomere copy number (T) to single copy gene (S) is referred as the T/S ratio and it is proportional to the average telomere length.

Quantitative PCR is a deeply standardized, reliable technique to measure telomere length when performed in controlled conditions[12].

6.2 Fagron TeloTest

Fagron TeloTest uses an automatized qualitative algorithm that calculates telomere length, infer biological age based on telomere length and according to estimated age acceleration and patient's anthropometric and physiological parameters recommends the most appropriate formula and lifestyle advice to delay the effect of ageing.

Unlike its numerous competitors, **Fagron TeloTest** is offered exclusively to practitioners that can value its usefulness in specific conditions like illness that runs in families. Telomere length testing is most informative in high-yield diagnostic settings, such as suspected cases of short telomere syndromes, genetic variation in telomere genes, and in the evaluation of bone marrow failure and related disorders.

Besides providing information about potential premature shortening, results from a telomere length test can be motivating for individuals who wish to adopt healthier lifestyles. **Fagron TeloTest** facilitates patients' individualized assessment through a medical questionnaire designed by healthcare professionals. This questionnaire includes questions about family longevity, cardiovascular risk, current physiological state (menopause, pregnancy), psychological state, food and environment, and known hypersensitivity to APIs and nutraceuticals ranked by the **Fagron TeloTest** algorithm. Comparison of chronological and biological age and treatment of patient questionnaire data allow the personalization of supplementation and health advice. These functions are evidence-based tools that support decision-making when considering treatment options and are based on the following literature:

Aging is characterized by an increase in the body's proinflammatory status with advancing age. This chronic, sterile (occurring in the absence of infection and primarily driven by endogenous signals), low-grade inflammation that occurs during aging is called "inflammaging"[13]. Lifestyle modifications such

as diet, exercise, and environmental enrichment have been found to elicit anti-inflammatory effects in aging[14]. For example, overfeeding or consuming diets high in saturated fats and refined sugars are known to robustly increase saturated fatty acids in the brain and neuroinflammatory responses[14], while other dietary strategies have been shown to reduce levels of neuroinflammation. Oxidative stress plays a crucial role in the development of age-related diseases[15] and antioxidant supplementation, such as resveratrol and vitamins, may positively affect the clinical damage induced by oxidative stress. Successful aging can be understood as the long-term maintenance of the ability to keep radical oxygen species production under control and retain antioxidant capacity[114].

Fagron TeloTest analyses quantitative data associated with the length of telomeres that tend to shorten with age. Quantitative data are obtained from a specific laboratory telomere length assay performed on DNA extracted from a buccal swab. In function of the result, **Fagron TeloTest** algorithm consults patient questionnaire and questionnaire-related tables (hypersensitivity, composites modifier by questionnaire) to block or/and rank the following APIs and nutraceuticals:

- **Vitamin D3**: A positive correlation between serum vitamin D and telomere length in humans has been evidenced in many studies[16-22], Vitamin D may reduce telomere shortening through anti-inflammatory and anti-cell proliferation mechanisms[23]. Supplementation with vitamin D3 has positive effect on telomere length[24], significantly reduces overall mortality among older adults[25-26] and protects from cardiac failure[27].
- **Folate (Vitamin B9)**: The concentrations of serum folate (Vitamin B9) have been positively linked to telomere length[28-33]. Furthermore, nutritional factors with antioxidant properties such as folate might act as modifiers of the associations between toxic metals and telomere length[34]. Low folate serum level seems associated with depression in elderlies[35].
- **Cyanocobalamin (vitamin B12)**: Older men and women are prone to vitamin B12 deficiency with associated subtle and different domain-specific disruptive effects in measures of memory and attention[36]. Low vitamin B12 serum level seems also to be associated with depression in elderlies[35]. The concentrations of vitamin B12 have been positively correlated with telomere length[32-33]. Vitamin B12 supplementation is strongly recommended to metformin users (see below).
- **Vitamin C (ascorbic acid)**: In the last decades, the understanding of vitamin C properties has undergone a major revolution, ranging from a simple antioxidant to a micronutrient, capable of epigenetic regulation[37]. Variation in ascorbate bioavailability can influence the demethylation of DNA and histones: in addition, ascorbate deficiency can present at different stages of aging and could be involved in the development of different age-related diseases. Higher vitamin C concentrations in plasma is associated with longer telomere length in normal elderly persons and suggest a protective role of these vitamins in telomere maintenance[38]. This finding is consistent with those showing that higher mineral and vitamin consumption is associated with longer telomeres among adults[39-41].
- **Vitamin E (tocopherols, tocotrienols)**: Intake of vitamin E has a beneficial effect on the prevention and management of chronic diseases including stroke, hypertension, diabetes mellitus, and fatty liver disease[42-43]. Meta-analysis of clinical trials revealed a beneficial effect of vitamin E supplementation, particularly in the form of α-tocopherol, on subclinical inflammation in adults[44-45]. Tocotrienols have a potential beneficial anti-ageing action with respect to cognitive impairment and DNA damage[46]. Furthermore, patients with an inadequate intake of vitamin E had shorter telomere length than those with an adequate intake[47].
- **Resveratrol:** Resveratrol is a natural phenol and a phytoalexin with very high antioxidant potential studied for its potential therapeutic use. In vitro experiments showed that resveratrol increases telomerase activity prevents senescence in human cells[48]. Supplementation of resveratrol extended the lifespan in various model organisms and extend the lifespan of mammals with impaired metabolism[49]. Resveratrol could prevent age-related ocular diseases and could protect the eyes against environmental factors[50].
- **Acetylcysteine:** Acetylcysteine is an established generic mucolytic and paracetamol poisoning antidote listed on the WHO Model List of Essential Medicines and a very popular dietary supplement for a number of other claims (sports supplement, protection against environmental toxins and pollutants, treat diverse conditions, increase testosterone levels...) in spite of limited scientific evidence[51]. Acetylcysteine can potentially be effective in aging-associated medical conditions. A meta-analysis showed a positive effect of acetylcysteine on human cognition, in healthy as well

as mentally ill individuals[52]. acetylcysteine may be helpful in chronic fatigue syndrome[53]. Topical NAC may prevent UV-associated photoaging of the skin[54]. Acetylcysteine (N-Acetyl L-Cysteine) is precursor to the amino acid L-cysteine and consequently the antioxidant glutathione (GSH). GSH is the most abundant intracellular free thiol, and its decrease has a crucial role in cell oxidative capacity. The synthesis of glutathione is decreased in the elderly, which increases oxidative stress, itself a propagator of aging. This effect can be reversed with dietary supplementation[55].

- **Astaxanthin**: Astaxanthin is a red carotenoid, found in shrimp, crab, salmon and algae, used as food colouring (E161J) in the industry. It has gained commercial interest as a health supplement due to its diverse biological activities[56-57]. Astaxanthin exerts a strong anti-oxidative activity by scavenging free radicals far superior to that of CoQ10[58]. There is a substantial body of evidence supporting the benefits of astaxanthin supplementation on skin health, especially for photoaged skin[59-60].
- **Omega-3:** Systemic reviews and meta-analyses show that omega-3 fatty acid supplementation effectively reduces triglycerides and might have a role in lowering the cholesterol of patients with familial hypercholesterolemia[61] thus reducing cardiovascular risk factors[62-65]. Omega-3 supplements also has a significant beneficial effect to prevent cognitive decline in the elderly[66].
- **Turmeric**: Turmeric is a plant with a long history of use in traditional medicine, especially for treating inflammatory conditions[67-68]. Its most important bioactive chemical constituents are curcuminoids, mainly curcumin. Curcumin has been extensively used in clinical trials and is showing positive outcomes for the treatment of aging-associated diseases.
- **Pomage:** Pomage is a substance Isolated from the dry extract of Malus pumila (bark and root) containing min 98% phloretin. Phloretin is a flavonoid with important antioxidant and anti-inflammatory biological activities and applications ranging from skin aging prevention to melanoma treatment[69].
- **Piperine**: Piper nigrum is one of the most popular spices in the world, with growing fame as a source of bioactive molecules with pharmacological properties. Its medical properties are mainly imputable to the alkaloid piperine that exerts anti-inflammatory, neuroprotective, immunomodulatory, cardioprotective, and anticancer effects[70-71].
- **Miodesin**™ is a patented phytocomplex from Fagron Pharmaceutical™ that has been shown to exert anti-inflammatory effects[72-74].
- **Pycnogenol**®: French maritime pine bark extract, a powerful antioxidant and natural anti-inflammatory, has shown to have promising effects in improving conditions including diabetes, cardiovascular health, osteoarthritis, sexual disorders, venous insufficiency, and neurological disorders including attention-deficit hyperactivity disorder and cognitive impairment[75].
- **Metformin**: Apart from being a safe, effective and globally affordable glucose-lowering agent for the treatment of diabetes, metformin has earned much credit in recent years as a potential anti-aging formula[76-78]. Metformin retards aging in model organisms, reduces the incidence of aging-related disease and attenuates telomere attrition. In humans, the anti-aging effect was reported in a population of diabetic subjects taking metformin who exhibits a significantly lower (7%) all-cause mortality than non-diabetics[79]. Using retrospective observational data, Bannister et al.[80] showed that T2DM patients treated with metformin had higher survival rates than patients treated with sulphonylurea and survival rates similar to (and, among those age > 70, even better than) their matched non-diabetic control group, despite the fact that the diabetic patients were more obese and had greater co-morbidities at baseline. Evidence has been also accumulated on a beneficial impact of metformin against many other aging-related morbidities (obesity, metabolic syndrome, cardiovascular disease, cancer, and cognitive decline)[81]. Several ongoing clinical trials (DEMFOS, VA-IMPACT, TAME, ePREDICE) are aimed to evaluate these additional benefits. The first publication of VA-IMPACT evidenced that metformin exerts tissue-specific effects on the expression of metabolic and non-metabolic human genes implicated in ageing[82]. However, the risks and benefits of extending metformin prescription to non-diabetic populations have yet to be fully elucidated. The decision to offer metformin treatment in older men 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. As metformin is associated with a higher risk of vitamin B12 and B6 deficiencies, which may result in an increased risk of cognitive dysfunction[83], B12 and B6 supplementation is strongly recommended to metformin users.

- **Testosterone**: Serum total and free testosterone levels in men decline gradually with advancing age. The trajectory of age-related decline is affected by comorbid conditions, adiposity, medications, and genetic factors. Testosterone treatment of older men with symptomatic testosterone deficiency offers some clinical benefits (e.g., improvement of sexual symptoms in men with low libido, correction of anemia) and is associated with low frequency of adverse events[84]. Today, a majority of testosterone prescriptions are written for men aged 40–64 years to fend off ageing even though testosterone is not approved by health authorities for age-related decline in testosterone. The decision to offer testosterone treatment in older men should be guided by an individualized assessment of potential benefits and risks including blood testosterone measurement and accompanied by a monitoring plan to optimize the benefit-to-risk ratio.
- **Cycloastragenol** (TA-65): Cycloastragenol is a triterpenoid saponin isolated from various legume species in the genus Astragalus. In vitro studies on human cells found that cycloastragenol may moderately increase telomerase activity and inhibit the onset of cellular senescence[85-88]. In mice, Cycloastragenol dietary supplementation leads to an improvement of certain health-span indicators, increases telomerase reverse transcriptase levels and elongates critically short telomeres[89]. Cycloastragenol treatment also partially rescued telomerase deterioration in antiaging protein Klotho null mutants, suggesting that KL plays a critical role in life-extension by regulating telomere length and telomerase activity[90]. In humans, Cycloastragenol taken orally significantly improved macular function[91] and showed a trend of improvements in telomere length compared with that of the placebo group[92]. Interventional studies in human beginning before the accumulation of age-related comorbidities are still lacking.
- **SiliciuMax™** is a maltodextrin-Stabilized Orthosilicic Acid. Among the various chemical forms of silicon available, orthosilicic acid is the form that presents greater bioavailability[93]. Silicon is a microelement that performs a number of important functions in the human body, being involved in the formation and maintenance of normal osteocartilaginous connective tissue, such as skin, hair, and nails, and having beneficial effects in the prevention of cardiovascular and neurodegenerative diseases[94]. Among the benefits of silicon supplementation are increased collagen and elastin synthesis, potentiating calcium fixation in bone tissue, promotion of nail hardness and stability, stimulation of hair fiber, which in addition to being more resistant to breakage also increases cord thickness, and maintenance of blood vessel elasticity[95-100].
- **Silymarin** (SM) is a standardized extract of the milk thistle seeds, a medicinal plant widely used in European medicine for over two thousand years, especially for treating liver disorders[101]. SM is also utilized in dermatological and cosmetic preparations for its antioxidant effect and well-described ability to reduce UVB- and chemically-induced damage that may result in skin carcinogenesis[102].
- **Pinetonina™** is a phytocomplex obtained from a blend of 3 essential oils (Lavandula angustifolia, Lavandula dentata and Foeniculum vulgare) indicated to reduce symptoms of stress, anxiety and insomnia[103].
- **Ginkgo Biloba** may play an important role in the prevention of vascular aging process[104] and macular degeneration[105].
- **GreenSelect** is a caffeine-free purified extract of catechins from tea enriched with high concentration (40%) of epigallocatechin-3 gallate (EGCG). Greenselect was shown to reduce body weight in subjects with obesity and metabolic syndrome and improve blood lipid profile and blood pressure[106-108].
- **Coenzyme Q10** (CoQ10), also known as ubiquinone, is the third most consumed dietary supplement after fish oil and multivitamins, and a potential candidate for the treatment of various diseases where oxidative stress plays a significant role[109-110]. CoQ10 levels decline with aging, and CoQ10 supplementation or topical application is associated with a statistically significant increase in total antioxidant capacity [111-113].

6.3. Risk assessment and post-market surveillance

Fagron TeloTest 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. All identified risks are adequately controlled and reduced to an acceptable level.

The accuracy of **Fagron TeloTest** relies on the accuracy of the telomere length and the inferred biological age determined through a specific laboratory assay and the relevance of nutritional advice associated with the calculated epigenetic age acceleration.

Laboratory protocol, calculation method and algorithm were reviewed by two evaluators with a degree in higher education (Ph.D.) and >5 years of experience in the relevant field. The protocol was validated using reference samples. Moreover, Fagron Genomics performs regular controls and organizes inter-laboratory comparisons with her sister company GX Sciences using the same standardized protocol.

Medical claims are based on common medical practice and supported by peer-reviewed publications. Treatment options and medical advice have been prepared by doctors and reviewed by Pharmacists. Scientific literature supporting these claims was assessed by our scientific team. A specific questionnaire (input), developed by medical doctors and pharmacists, contributes to the patient's individualized assessment, considering possible contraindications and allowing the personalization of supplementation and health advice.

The integration of these medical elements as output or output within the **Fagron TeloTest** algorithm has been supervised by our medical team. The first medical reports were systematically reviewed by medical doctors and random medical check are regularly performed.

The safety of **Fagron TeloTest** has been evaluated through more than three years of clinical experience that revealed a high degree of customer satisfaction and a very low level of clinically relevant complaints. More than 800 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 400 tests in the last 12 months and the projection for 2022 is around 500 tests as the company has entered new markets and the test has been launched early 2022 in the USA by our partner GX sciences (a Fagron company). The amount of post-marketing follow-up data is now considerable and indicates that **Fagron TeloTest** does not pose an increased risk for the user.

The very low level of clinically relevant complaints and the high degree of customer satisfaction show that recommended treatment options are well accepted by healthcare professionals and that pharmaceutical formulas are tolerated by patients.

7. CONCLUSIONS

Fagron TeloTest is an innovative algorithm that calculates telomere length, infer biological age based on telomere length, interpret result and relevant patient's anamnesis to recommend the most appropriate formulas and advice to delay the effect of ageing.

- **Telomere testing for healthcare professionals**
  Fagron TeloTest detearmines whether a male or female subject has reduced telomere length, a marker of epigenetic age acceleration related to diseases or an unhealthy lifestyle. Knowing the rate of telomere loss allows adjustments to be made in nutrition and lifestyle that can slow aging and age-related diseases.
- **Personalizing advice and supplementation**
  Nutritional advice, selected from the most authoritative resources on nutritional value, dietary supplements, herbal medicines, and complementary therapies, has been reviewed by medical doctors, nutritionists and pharmacists.
- **Minimizing the risks of intolerance or contraindications**
  The patient questionnaire of **Fagron TeloTest** has been elaborated by medical doctors and pharmacists to minimize risks of intolerance or contraindications.
- **Patient satisfaction**
  The high degree of customer satisfaction, and the very low level of clinically relevant complaints indicate that the clinical base of **Fagron TeloTest** is well-founded, and personalized advice and supplements well accepted by healthcare professionals and pharmaceutical formulas tolerated by patients.
- **Clinical safety and performance**
  The analysis of risk management, scientific literature review, and post-market experience with the evaluated device confirms the clinical safety and performance of **Fagron TeloTest**. The test shows conformity by achieving the intended performance under normal conditions of use when weighing known or foreseeable risks and adverse events against the benefits of the intended performance.

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