Fagron Sport

Genetic report

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Fagron genomics

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REPORT CONTENT

1.

Patient identification data

Requesting physician :	**Demo Doctor Genomics**
Physician email :	**demo_doctor@fagrongenomics.com**
Patient name :	**Demo Woman Patient Genomics**
Gender :	**Woman**
Date of birth :	**01-01-1991**
Sample type :	**buccal swab**
Sample code :	**SPR00002AA**
Sample date :	**17-11-2022**
Report date :	**17-11-2022**

2.

Presentation of Fagron Sport

2. Presentation of Fagron Sport

What is Fagron Sport?

Fagron Sport is a genetic test that analyzes DNA to evaluate 16 genetic variants with the intention of informing about predispositions and risks associated with individual athletic performance. This information should be integrated with physical (eg, age, gender, body mass index, VO2 max, etc.) and behavioral (eg, eating habits, physical activity, etc.) characteristics to establish the best personalized training plan.

Who is it addressed to?

Fagron Sport is a test aimed at health professionals and specialists in sports medicine.

For what type of patient?

Fagron Sport is designed for people who practice sports, both privately and professionally. Thanks to the study of our genetics we will be able to know and evaluate our sports possibilities and also our limitations, prevent injuries, improve our performance, and ultimately take care of our health.

How do you evaluate genetic variants?

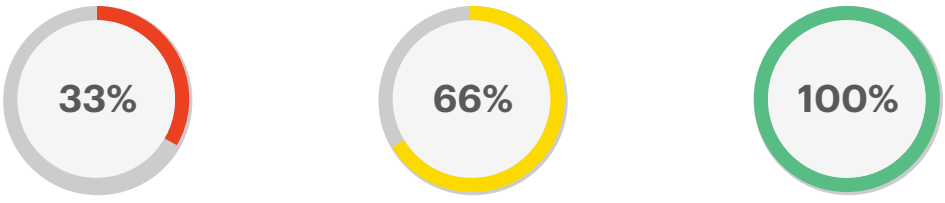
Fagron Sport evaluates the genetic variants analyzed, classifying them as "favourable", "intermediate" and "unfavourable":

Favorable genotype Intermediate genotype Unfavorable genotype *

* Having an "unfavorable" genotype doesn't mean someone can't exercise normally, it just suggests that they might struggle more than someone with a more favorable genotype.

How do you evaluate the categories?

Fagron Sport assigns a value to each genotype and calculates the total value per category (eg “muscular properties”, “power”, etc.) represented by an accelerometer.

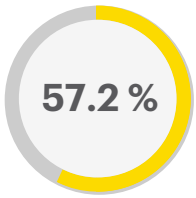


3.

Sports skills

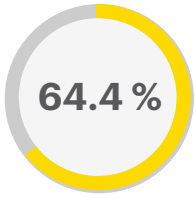
3. Sports skills of the patient

1. Power (anaerobic exercise)



Gene	SNP (transition)	beneficial allele	Patient genotype	Effect
ACTN3	rs1815739 (C > T)	C	CC	
AGT	rs699 (G > A)	G	AG	
PPARGC1A	rs8192678 (T > C)	T	CC	
HIF1A	rs11549465 (T > C)	T	CT	
AMPD1	rs17602729 (G > A)	G	AG	
LRPPRC	rs10186876 (A > G)	A	AA	

2. Endurance (aerobic exercise)

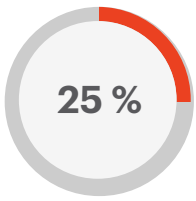


Gene	SNP (transition)	beneficial allele	Patient genotype	Effect
PPARGC1A	rs8192678 (C > T)	C	CC	
HIF1A	rs11549465 (T > C)	T	CT	
AMPD1	rs17602729 (G > A)	G	AG	
AQP1	rs1049305 (C > G)	C	CG	
ADRB2	rs1042713 (A > G)	A	AG	
COL5A1	rs12722 (T > C)	T	CT	

3. Power vs. Endurance

According to the results of power and resistance, the global predisposition of the patient is:

4. Aerobic potential (VO2 max)



Gene	SNP (transition)	beneficial allele	Patient genotype	Effect
PPARGC1A	rs8192678 (T > C)	T	CC	
HIF1A	rs11549465 (T > C)	T	CT	
AMPD1	rs17602729 (G > A)	G	AG	
ADRB2	rs1042713 (A > G)	A	AG	
PPARD	rs2267668 (A > G)	A	AG	
ZIC4	rs11715829 (C > T)	C	TT	

Aerobic fitness (cardiovascular endurance) is the body's ability to supply oxygen to the muscles, allowing them to work or participate in physical activity. The VO2 max test is the most accurate test of aerobic or cardiovascular fitness. Studies based on the measurement of VO2 max have identified SNPs in genes related to the development of the cardiovascular system associated with maximal gains in VO2 max from exercise.

Calculation of the VO2 max

The best and most precise method to determine the VO2max value is a breath analysis. An alternative less precise is the Copper test, a 12-minute run that measures the maximum distance covered during that time. The VO2max value can then be determined using the following formula:

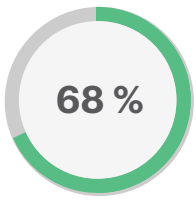
VO2max = (distance traveled in meters - 505) / 45

You can use this table to estimate your VO2 max value using the Cooper test:

Age	Very bad	Bad	Regular	Good	Excellent	Higher
13-19	< 25,0	25,0 - 30,9	31,0 - 34,9	35,0 - 38,9	39,0 - 41,9	> 41,9
20-29	< 23,6	23,6 - 28,9	29,0 - 32,9	33,0 - 36,9	37,0 - 41,0	> 41,0
30-39	< 22,8	22,8 - 26,9	27,0 - 31,4	31,5 - 35,6	35,7 - 40,0	> 40,0
40-49	< 21,0	21,0 - 24,4	24,5 - 28,9	29,0 - 32,8	32,9 - 36,9	> 36,9
50-59	< 20,2	20,2 - 22,7	22,8 - 26,9	27,0 - 31,4	31,5 - 35,7	> 35,7
60+	< 17,5	17,5 - 20,1	20,2 - 24,4	24,5 - 30,2	30,3 - 31,4	> 31,4

Table Reference: The Physical Fitness Specialist Certification Manual, The Cooper Institute for Aerobics Research, Dallas TX, revised 1997 printed in Advance Fitness Assessment & Exercise Prescription, 3rd Edition, Vivian H. Heyward, 1998.p48

5. Response to exercise



There is considerable individual variability in the response to similar exercise training and genetic variants may play an important role in this variability. Some individuals are 'low responders' (improving their fitness only slightly following a specific exercise training) while others respond well or very well ('high responders').

Gene	SNP (transition)	beneficial allele	Patient genotype	Effect
AGT	rs699 (G > A)	G	AG	
ADRB2	rs1042713 (A > G)	A	AG	
PPARD	rs2267668 (G > A)	G	AG	
IL1B	rs1143634 (G > A)	G	GG	
OPRM1	rs1799971 (A > G)	A	AA	

4.

Physical characteristics

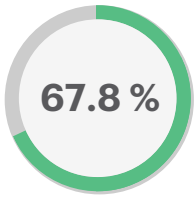
4. Physical characteristics of the patient

1. Inflammation

Gene	SNP (transition)	beneficial allele	Patient genotype	Effect
IL1B	rs1143634 (G > A)	G	GG	

Several genetic variations enhance the inflammatory response that allows slow repair of muscle damage after exercise.

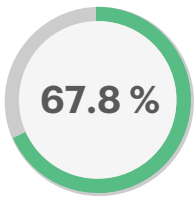
2. Muscle properties



Gene	SNP (transition)	beneficial allele	Patient genotype	Effect
ACTN3	rs1815739 (C > T)	C	CC	
PPARGC1A	rs8192678 (T > C)	T	CC	
OPN	rs28357094 (G > T)	G	GG	

Skeletal muscle contains a heterogeneous composition of different fiber types. This composition is an inherited trait that may partly predict athletic performance.

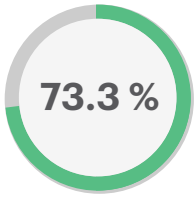
3. Soft-tissue injuries



Gene	SNP (transition)	beneficial allele	Patient genotype	Effect
ACTN3	rs1815739 (C > T)	C	CC	
COL5A1	rs12722 (C > T)	C	CT	
MMP-3	rs679620 (T > C)	T	CT	

Increased physical activity puts a lot of pressure on tendons and muscles. This can cause injury to the tendons (tendinopathy) and muscles. Numerous scientific studies have linked a series of genes with an increased risk of tendinopathy and/or muscle injury.

4. Post-Exercise Recovery



Gene	SNP (transition)	beneficial allele	Patient genotype	Effect
AMPD1	rs17602729 (G > A)	G	AG	
SLC16A1	rs1049434 (T > A)	T	TT	

On average, a muscle needs 24 to 48 hours to recover and repair the tissues that have been worn out during exercise or training. If the individual has slow clearance of lactate from the muscles, recovery time may be longer after intense physical exercise.

5.

Understand genetics

5. Understand genetics

Before reading this full report, please take a moment to read this overview to better understand the results and guide you on how best to use the Fagron Nutri-Sport results.

What is a genetic variant?

DNA is the "instruction manual" that governs the functioning of the human body. This "instruction manual" consists of long strands, containing many individual units called "genes", which in turn are made up of pairs of molecules called "nucleotides".

Each gene is comprised of thousands of combinations of four nucleotides that make up our genetic code: A, T, C, and G.

Nucleotides are the "spelling" that determine the function of each gene. The sequence formed by these bases varies between people. For example, at a specific location in a sequence, 80% of the population might have a “T”, while the other 20% may have an “G”. This specific difference of only one base, is called a Single Nucleotide Polymorphism or SNP.

SNPs are the most common type of genetic variation among people. Most SNPs have no effect on health or development. However, some create individual differences that influence how we look, and others create functional differences or affect biochemical reactions that are important for our long-term health and well-being.

What is an allele and a genotype?

An allele is each of two or more versions of a gene or SNP. The sum of the two alleles of an individual for a given position forms the genotype. If the two alleles are identical (example: AA), the genotype is homozygous for this position. If the two alleles are different (example: AG), the individual is heterozygous for this position.

An allele that creates an individual difference (phenotype) can be dominant, semi-dominant, or recessive:

- **Dominant:** the effect of one allele on a heterozygous genotype completely masks the effect of the other.
- **Semi-dominant:** the phenotype of the heterozygous genotype is different from and often intermediate to the phenotypes of the homozygous genotypes.
- **Recessive:** the phenotype of the heterozygous genotype is not different from the phenotype of the homozygous wild type, two copies are necessary to obtain the phenotype studied.

What does it mean to have an unfavorable genotype?

Having an 'unfavourable' genotype does not mean that someone cannot play sports normally, it simply suggests that they may have more difficulties than someone with a more favorable genotype.

What is this genetic test based on?

This test is based on different genetic studies accepted by the scientific community. Section 8 indicates the main studies on which it is based.

6.

Methodology

6. Methodology

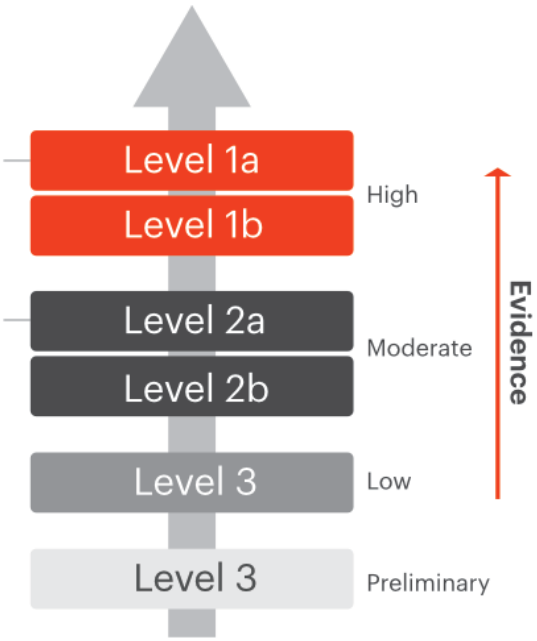
How were the genetic variants selected and evaluated?

Fagron Sport was developed by a multidisciplinary team of medical doctors, 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.

The following selection criteria were 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.

Only genetic variants from level 1A to 2A were selected.



How was it analyzed?

The DNA was extracted from the buccal swab sample you provided and was analyzed by our clinical analysis laboratory. DNA was extracted using the KingFisher Flex® robotic extraction system (Thermo Fisher Scientific). The study of the genetic variants was carried out using a DNA biochip designed to measure for the chemiluminescent detection of each of them using TaqMan® technology. TaqMan® technology for genotyping testing is proven and widely used in clinical and research settings.

What are the limits of this report?

- Each genetic marker tested is only one factor that predicts the probability of a particular result. However, your lifestyle, diet, and the environment you are exposed to all impact the ultimate effect predicted by your genes. These external factors cannot be considered in this report.
- For any questions about your health or personal clinical situation, you are advised to consult a qualified health professional.
- The information in this report is not used to diagnose genetic diseases or abnormalities, as it does not predict the risk and likelihood of certain genetic outcomes. It is also not intended to treat, diagnose, or cure any medical condition or disease.
- Our clinical laboratory has standard and effective procedures to protect against technical and operational problems. However, problems may occur in the shipment to the laboratory or in the handling of the sample, including, but not limited to, damage to the sample, mislabeling, and loss or delay in receiving the sample. In such cases, the medical laboratory may need to request a new sample.
- As with all medical laboratory tests, there is a small chance that the laboratory may provide inaccurate information.
- It is the responsibility of the professional who requests a test from us to guarantee the interested party appropriate genetic counseling in accordance with Law 14/2007, of July 3, on Biomedical Research.
- Fagron Genomics, S.L.U. declines all responsibility derived from the use and interpretation of the results of our tests by the requesting health professional.
- Fagron Genomics, S.L.U. does not access data identifying the patient from whom the sample comes, so it is also the responsibility of the requesting professional to comply with the applicable data protection regulations.

7.

Analyzed genes

7. Analyzed genes

The detailed interpretation of the genetic study is attached. All evidence is supported by scientific articles indexed in PubMed (http://www.ncbi.nlm.nih.gov/pubmed), identified in July 2022.

Gene (SNP)	Description
MMP-3 (rs679620)	The matrix metalloproteinase-3 (MMP-3) is involved in the breakdown of extracellular matrix proteins and during tissue remodeling in normal physiological processes. The GG genotype of rs679620 polymorphism in MMP3 is associated with an increased risk of Achilles tendinopathy, while the AA and AG genotypes were associated with a reduced risk to Achilles tendon rupture [14, 59, 83, 95].
OPRM1 (rs1799971)	The rs1799971 polymorphism in the μ-opioid receptor gene (OPRM1) was related to changes in norepinephrine, lactate, and rate of perceived exertion and pain during exercise [99-100]. The general function of norepinephrine is to mobilize the brain and body for action. Athletes carrying at least one minor G allele were characterized by higher sensitivity when compared with AA wild-type homozygotes [78, 99-100].
IL1B (rs1143634)	The Interleukin 1 beta (IL1B) is an important mediator of the inflammatory response. The T allele of the rs1143634 polymorphism in the IL1B gene is associated with the inflammation of skeletal muscle following acute exercise that may potentially affect exercise adaptations and pain perception [77-78].
OPN (rs28357094)	A polymorphism in the promoter of the osteopontin (OPN) gene (rs28357094) has been associated with multiple inflammatory states, severity of Duchenne muscular dystrophy and muscle size [96-97]. The G allele is associated with an increase in muscle volume [96, 98].

Gene (SNP)	Description
SLC16A1 (rs1049434)	During exercise, muscle fibers produce and accumulate lactate and hydrogen ions (H+) that may result in acute reduction in force and power (muscle fatigue). The H+-monocarboxylate cotransporter MCT1, encoded by the SLC16A1 gene, facilitates their removal by uptaking them into oxidative muscle fibers where lactate can be used as respiratory fuel [120-121]. A common MCT1 missense mutation (rs1049434) is associated with a strong reduction of lactate transport rate: Carriers of the T allele have a slower lactate transport rate and exhibit a higher lactate accumulation during high-intensity effort [122-124].
ACTN3 (rs1815739)	α-actinin plays a decisive role in muscle contraction, acting as an anchor point or organizing center for the preformation of actin filaments. α-actinin 3 (ACTN3) is expressed only in fast-twitch muscle fibers, where it plays an important role in the generation of explosive and powerful muscle contractions. A common genetic variant in the ACTN3 gene (rs1815739 C>T) causes about 20% of the population with the TT genotype not to produce fast-twitch muscle fibres [7]. This mutation, also termed R577X, is not associated with any disease phenotype but affects athletic performance and muscle phenotypes. The C allele (R) is associated with increases in muscle strength and thickness in response to training [8-10], while the T allele (X) is associated with poorer sprint and power performance [11-15]. Carriers of the TT (XX) genotype are more susceptible to exercise-induced muscle damage [16-19].
AGT (rs699)	The renin-angiotensin system is a hormonal system that regulates blood pressure, extracellular body volume, and sodium and potassium balance. The rs699 C>T polymorphism, also known as M235T, of the Angiotensinogen (AGT) gene is associated with higher plasma angiotensin concentrations [29-31], higher blood pressure and increased risk for hypertension [29, 32], which are higher in individuals homozygously carrying the C allele (C/ C) or heterozygous (C/T) than in individuals carrying the T allele in homozygosity (TT). The C allele exerts a favourable effect on power performance by promoting skeletal muscle hypertrophy [12, 33-34]. It favourably modifies the influence of training or exercise on various health-related fitness parameters, such as cardiorespiratory endurance, blood pressure, and heart morphology [35-39).
PPARGC1A (rs8192678)	PPARGC1A (or PGC-1α) regulates critical processes in muscle physiology, including mitochondrial biogenesis, lipid metabolism, angiogenesis, and the conversion of muscle fiber type towards slow-twitch type I fibers [111]. The PPARGC1A rs8192678 G>A polymorphism results in the substitution of glycine with serine in codon 482 (Gly482Ser). The minor A-allele (coding a serine residue) results in lower protein levels and reduced activity of the PPARGC1A protein [112]. The PPARGC1A rs8192678 polymorphism has been associated with athlete status in numerous publications [113]. Although the A (Ser) allele may impair aerobic capacity [103], it was shown to be more favorable for power athletes compared to controls [114-115]. The G (Gly) allele may be considered a beneficial factor for endurance performance [116-117]. A-allele carriers (Ser482) exhibit superior health benefits in increasing the VO2 max values when engaging in a physically active lifestyle compared to G-allele carriers (Gly482) [104, 118]. Carriers of minor A-allele (Ser) lacks a training-induced increase in the content of slow contracting oxidative fibers[119].

Gene (SNP)	Description
HIF1A (rs11549465)	The transcription factor HIF1A, induced in the presence of low oxygen concentrations, plays an essential role in the physiological response to hypoxia. The allele variant T (Ser482) of the HIF1A rs11549465 polymorphism has been shown higher transcriptional activity under hypoxic conditions when compared with the wild allele C [73]. The T allele is associated with advantages in power sports, as well as a tendency to gain muscle mass and reduce body fat, which is consistent with the greater muscle mass of strength/power athletes [42, 74-76]. Genetic factors that influence individual fibrogenic response to hypoxia in the subcutaneous tissue may also play a crucial role in the pathogenesis of cellulite. The rare T allele of HIF1A rs11549465 has been shown to have a protective role against the development of cellulite [8].
AMPD1 (rs17602729)	The muscle-specific enzyme adenosine monophosphate deaminase 1 (AMPD1) is a very important regulator of muscle energy metabolism during exercise. The nonsense mutation (Gln12X, rs17602729) of the AMPD1 gene converts glutamine codon (CAA) into the premature stop codon (TAA), which results in the early interruption of protein synthesis. The TT genotype leads to a complete deficiency of the AMPD1 protein, which impairs AMP metabolism leading to muscle fatigue, weakness, and cramps, as well as a decreased exercise capacity, a lower response to exercise, and a lower relative increase in peak VO2 after aerobic training [40-41]. In contrast, the GG genotype has been associated with physical performance in power sports [42-46]. Carriers of the T allele have a limited training response of ventilatory phenotypes during maximal exercise [40, 47] and a reduced submaximal aerobic capacity [41]. The TT genotype, with a complete AMPD1 deficiency, have an impaired AMP metabolism leading to muscle fatigue, weakness, and cramps, as well as a decreased exercise capacity and a lower response to exercise [40-41].
LRPPRC (rs10186876)	LRPPRC is a multifunctional protein considered essential for the assembly of the mitochondrial oxidative phosphorylation system, and therefore for energy production [92]. The rs10186876 LRPPRC polymorphism has been associated with handgrip strength, a widely used indicator of muscular fitness [93] and with weightlifting performance [94].
ADRB2 (rs1042713)	The β2 adrenergic receptor, also known as ADRB2, binds adrenaline, a hormone and neurotransmitter whose signaling mediates physiologic responses such as smooth muscle relaxation and bronchodilation. The Gly16Arg substitution (rs1042713 G>A) in ADRB2 has been shown to regulate the cardiopulmonary response to exercise [20]. rs1042713 influences elite endurance performance status, with the G (Gly) allele exerting an unfavourable effect [21-23]. Arg16 variant (A allele) showed a higher peak VO2max compared with Gly16 carriers [21, 24-25]. rs1042713 also influences exercise-induced fat loss and improvement of metabolic profile, with the G (Gly) allele exerting an unfavorable effect [26-28].

Gene (SNP)	Description
AQP1 (rs1049305)	AQP1 encodes a small integral membrane protein which function as both a water channel and a non-selective monovalent cation channel when activated by intracellular cGMP. During osmotic stress, such as occurs during intense exercise, AQP1 facilitates water transfer from blood to muscle, provides osmotic protection, and promotes water reabsorption. The CG and CC genotypes of AQP1 rs1049305 polymorphism are associated with faster long-distance running performance [48- 52]. The presence of the G allele may result in a slower response to changes in osmotic gradients during exercise.
COL5A1 (rs12722)	The COL5A1 gene encodes the α1 chain of type V collagen that exerts a crucial role in the regulation of the size and configuration of other abundant fibrillar collagens supporting many tissues in the body, such as tendons, ligaments, and muscles [53]. A common C to T transition within the COL5A1 3′ untranslated region (rs12722) may alter COL5A1 mRNA stability and thereby reduce the production of type V collagen [54]. Individuals with a TT genotype would have increased type V collagen production and thus favorably altered mechanical properties of tendons, which enhances endurance running ability [55-56]. The T allele (TT+TC) was associated with an increased risk of ligament and tendon injuries [57-59].
PPARD (rs2267668)	The Peroxisome proliferator-activated receptor beta PPARD, also known as NR1C2, is a nuclear hormone receptor that governs a variety of biological processes. In muscle, PPARD expression is increased by exercise, resulting in increased oxidative (fat-burning) capacity and an increase in type I fibers. Genetic variations in PPARD determine mitochondrial function and change in aerobic physical fitness and insulin sensitivity during lifestyle intervention [101-102]. The PPARD rs2267668 G allele was associated with a negative response to aerobic training (decrease in VO2 peak) [102-103]. A allele carriers may enjoy fewer beneficial effects of exercise-centered lifestyle intervention on anthropometric indices and blood measurements [27, 104].
ZIC4 (rs11715829)	The rs11715829 polymorphism in the gene encoding the zinc finger protein ZIC4 is associated with gains in maximal O2 uptake (V̇o2max) after exercise training, with the major allele homozygotes (TT) gaining ~30% less than the minor allele carriers [136-137].

8.

References

8. References

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