

- Patient's name: Patient Man Imcas 2023
- Sample code: FILL00216AA
- Report date: 26-01-2023



## Fagron FillerTest

Unique genetic approach for filler treatments

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## FillerTest Genetic report

### LEGAL DISCLAIMER

Fagron Genomics, S.L.U. performs genetic tests, at the request of health professionals, in relation to biological samples from patients obtained by the health professional. Our tests do not replace a medical consultation, nor do they constitute a diagnosis or treatment, nor should they be interpreted as such. Only a healthcare professional can interpret the results of such tests, based on his or her knowledge of the patient's medical history and other relevant factors, and, under his or her responsibility, make a diagnosis or prescribe treatment to the patient. We disclaim all liability arising from the use and interpretation of our test results by the requesting healthcare professional. Fagron Genomics, S.L.U. expressly reserves the right to take appropriate legal action in the event of improper, negligent or incorrect interpretation and/or use of the results of our tests. It is the responsibility of the professional requesting a test to guarantee the interested party appropriate genetic counselling in accordance with Law 14/2007, of 3 July, on Biomedical Research. Fagron Genomics, S.L.U. does not have access to the identifying data of the patient from whom the sample is taken, so it is also the responsibility of the professional requesting the test to comply with the applicable data protection regulations.

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## 1. Patient identification data



|                      |     |                               |
|----------------------|-----|-------------------------------|
| Requesting physician | —●— | <b>Doctor Imcas 2023</b>      |
| Contact              | —●— | <b>doctor@imcas2023.com</b>   |
| Patient's name       | —●— | <b>Patient Man Imcas 2023</b> |
| Sex                  | —●— | <b>Male</b>                   |
| Date of birth        | —●— | <b>05-03-1990</b>             |
| Sample code          | —●— | <b>FILL00216AA</b>            |
| Sample date          | —●— | <b>26-01-2023</b>             |
| Report date          | —●— | <b>26-01-2023</b>             |



## 2. Patient results

| HLA combinations                                   | Result  |
|--|---|
| Combination HLA subtype B*08 + HLA subtype DRB1*03 |  |

Genetic data validated by:  
Fagron Genomics Laboratory  
Data interpretation is under the responsibility of BSure Medicals B.V

The combination of the HLAs DRB1\*03 and B\*08 (red) was associated with an almost 4-fold increase in the odds of developing immune-mediated rejection reactions to fillers<sup>4</sup>.

A negative result for this combination (green) does not completely exclude the risk of late onset of side effects, however this probability will be very low.

### INDICATIONS



NO combination



Combination



### **3. Why is genetic testing relevant for filler treatments?**

Not all treatments work and/or have the same effect for everyone. By using genetics, we can be much more accurate and effective in treating, understanding and preventing all kinds of conditions and/or diseases. The study of genetics has ushered in a new era of preventive and personalized medical treatment.

In the Netherlands there are an average of 150,000 filler treatments per year, with approximately 500 to 600 complications occurring<sup>1</sup>. Fortunately, these are few complications. There are many discussions and different studies about how many complications there are, ranging from 0.4% to 4%<sup>2</sup>. In addition, it is suspected that many complications are not reported to cosmetic clinics or doctors because these reactions often occur many months or years after treatment and are therefore not associated with the fillers. In general, filler treatments are safe and there are few complications, thanks in part to increasingly better materials (temporary hyaluronic acid fillers) and an increase of highly skilled and trained doctors. The question remains, however, how your own genetic predisposition can have an influence on possible complications with filler treatments.

Professor Jaume Alijotas Reig (MD, PhD), expert in immunology, head of the research department of immune diseases and internist at the university hospital Vall d'Hebron in Barcelona, has spent years researching immune diseases. He discovered that a small group of his patients with fillers had complaints that were caused by a strong reaction of their own immune system to the fillers. It was striking that other people with the same filler treatment had no complaints. Further research in collaboration with two university hospitals in the Netherlands showed that there is a genetic predisposition that gives an increased risk of the violent reactions of the own immune system to fillers<sup>3</sup>.

The results obtained in collaboration with Dr. Tom Decates, cosmetic doctor KNMG (researcher at Erasmus MC in Rotterdam), and Dr. Frank Niessen, plastic surgeon (researcher at AUMC in Amsterdam) were published in a scientific article early 2021<sup>4</sup>.

For further details about this research, please consult the scientific article<sup>4</sup>.



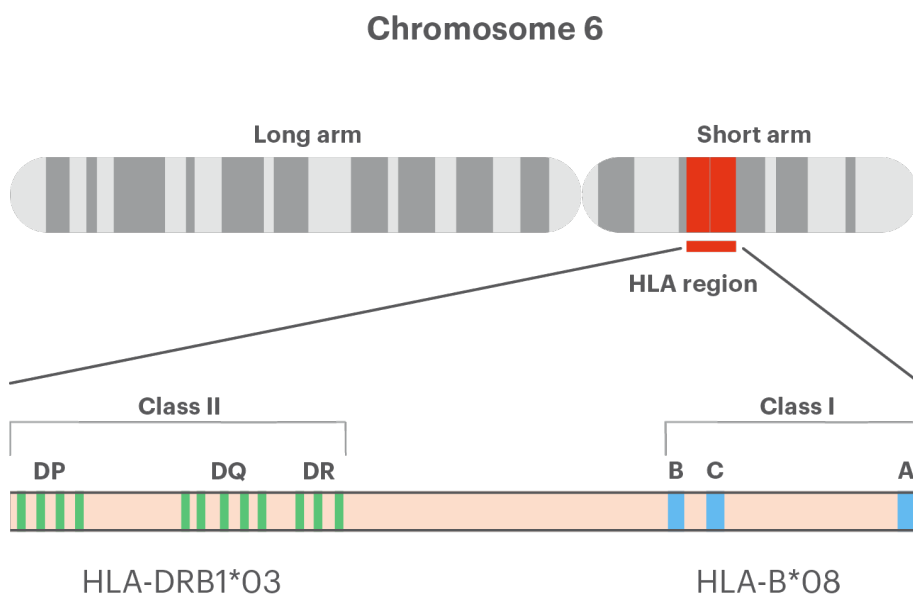
## 4. What do we detect with the test?

Everyone has specific immune cell receptors on the outside of the cells. These are so-called HLAs: Human Leukocyte Antigens. These are part of the human immune system. The HLAs can recognize whether something is natural or foreign. They ensure that your body recognizes and attacks a bacteria or virus, so that your body remains healthy.

Fagron FillerTest for fillers is aimed at finding out which genetic predisposition you have for the HLAs. The before mentioned scientific study showed that the combination of the HLAs DRB1\*03 and B\*08 causes an increased risk of immune-mediated rejection reactions to fillers. Fagron FillerTest determines whether someone has this combination of HLAs

A negative result for this combination (green) does not completely exclude the risk of late onset of side effects, however this probability will be very low.

These HLAs are located on the short arm of chromosome 6, as illustrated in the image below. There are more than a million combinations and thus different HLA typologies. Analysing and detecting a specific combination of HLAs is therefore a complex and expensive process.





## 5. Types of complications

Complications could be divided in two big groups

### Mild short term complications

Days/weeks after the filler treatment, mild, temporary complications may occur, such as local inflammation or irritation. These complications usually disappear after a few weeks or are treatable

### Complex long term complications

More serious and complex complications can manifest themselves 3 to 6 months after treatment, but also only after 5 to 8 years. These complications are caused by a violent reaction of the own immune system to fillers. These are so-called late-onset immune-mediated side effects. As mentioned before, the chance of these reactions is small, but the consequences are complex and serious. It can cause chronic complaints that must be monitored and treated for months, years or in some cases lifelong. Fagron FillerTest is aimed at determining the genetic predisposition that gives an increased risk of having these complications.

The following table provides an overview of these two groups of complications, as well as those targeted by Fagron FillerTest (the late-onset immune-mediated reactions).

| Local/Regional  |   | Systemic  |  | Severe ++ |
|---|---|---|--|-----------|
| Immediate   | Intermediate  | Late-onset  |  |           |
| <ul style="list-style-type: none"> <li>• Pain</li> <li>• Oedema</li> <li>• Ecchymosis</li> <li>• Pigmentation</li> <li>• Pruritus</li> <li>• Elevation</li> <li>• Embolism</li> <li>• Erythema</li> </ul> | <ul style="list-style-type: none"> <li>• Swelling</li> <li>• Nodules</li> <li>• Fistulisation</li> <li>• Abscesses</li> <li>• Necrosis</li> <li>• Scars</li> <li>• Granuloma</li> <li>• Pigmentation</li> </ul> | <ul style="list-style-type: none"> <li>• Induration</li> <li>• Oedema</li> <li>• Nodules</li> <li>• Granuloma</li> <li>• Pigmentation</li> <li>• Pseudo abscess</li> <li>• Combination of them</li> </ul> | <ul style="list-style-type: none"> <li>• Sarcoidosis</li> <li>• Granulomatosis</li> <li>• Systemic sclerosis</li> <li>• Panniculitis</li> <li>• Hepatitis</li> <li>• Pneumonitis (acute/chronic)</li> <li>• Sjogren syndrome</li> <li>• Human Adjuvant Dis</li> <li>• Multisystemic fafilure</li> <li>• Primary Biliary Cirrhosis</li> <li>• Vasculitis</li> <li>• Fibromyalgia /C.F.S.</li> </ul> |           |

*Delayed immune mediated severe adverse events.  
3 -6 to 60 months after implanting*





## 6. Test procedure

### Fagron Genomics Laboratory

The sample will be sent to and analysed by the Fagron Genomics clinical laboratory in Terassa, Barcelona (Spain). Fagron Genomics (fagrongenomics.com) is part of the multinational Fagron B.V., a pharmaceutical company headquartered in Rotterdam, the Netherlands.

### Methodology

The analysis is conducted using buccal epithelial cells that are collected by scraping the inner side of the cheeks using a swab. DNA is extracted using the KingFisher Flex® robotic extraction system (Thermo Fisher Scientific). HLA-B and HLA-DRB1 alleles are amplified by PCR and HLA- sequence-specific oligonucleotide genotyping is performed by flow cytometry (Luminex technology). Luminex technology requires a specially pure sample with DNA concentrations ranging from 30 to 50 ng/µl (quantified by Thermo Scientific™ NanoDrop™) to avoid interactions with cellular debris that may alter the results. Since the genotype of interest here is the combination of both alleles, the analysis is performed one allele at a time: First, HLA-B is genotyped and if the result is positive for HLA-B\*08, then HLA-DRB1 is analyzed.

The Fagron FillerTest algorithm is an IVD CE self-declared product, manufactured by BSure Medical B.V., in accordance with IVDD (98/79/EEC).

## 7. References

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2. Karim RB, Hage JJ, van Rozelaar L, Lange CA, Raaijmakers J (2006) Complications of polyalkylimide 4% injections (Bio-Alcamid): a report of 18 cases. *J Plast Reconstr Aesthet Surg* 59: 1409-1414. • Nelson L, Stewart KJ. (2011) Early and late complications of polyalkylimide gel (Bio-Alcamid®). *J Plast Reconstr Aesthet Surg* 64: 401-404. • Schelke LW, van den Elzen HJ, Canninga M, Neumann MH (2009) Complications after treatment with polyalkylimide. *Dermatol Surg* 35: 1625-1628. • Artzi O, Loizides C, Verner I, Landau M. (2016) Resistant and Recurrent Late Reaction to Hyaluronic Acid-Based Gel. *Dermatol Surg*. 42: 31-37.
3. <https://data.epo.org/publication-server/pdf-document?pn=2564197&ki=B1&cc=EP> ; European patent "A METHOD FOR DETECTING THE SUSCEPTIBILITY TO DEVELOP ADVERSE SIDE EFFECTS RELATED TO BIOIMPLANTS".
4. Decates TS, Velthuis PJ, Schelke LW, Lardy N, Palou E, Schwartz S, Bachour Y, Niessen FB, Nijsten T, Alijotas-Reig J. (2021) Increased risk of late-onset, immune-mediated, adverse reactions related to dermal fillers in patients bearing HLA-B\*08 and DRB1\*03 haplotypes. *Dermatol Ther*. 34: e14644.

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Together

we create the future  
of personalizing medicine.

