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Paolo Marandola
Ivan Marandola
Nicola Locorotondo

Molecules of Life

Introduction to prediventive, regenerative
and personalized health medicine

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info@aracneeditrice.it

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info@gioacchinoonoratieditore.it

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PART I

THE PROFILING PROCESS

Individual assessments and profile cards

Self-assessment is an overall evaluation of the quality of life. It is more effective than any other evaluation carried out by a doctor and/or by instrumental/biological tests. Subjectivity against objectivity: this is the real distinctive feature of personalized medicine, which is based on the individual: «This is my body, my health and my life», unlike conventional medicine, where the doctor analyzes, evaluates and takes a decision, often in contrast with the patient's feelings and wishes, «You cannot understand, I am the doctor and I know what is right, be quiet».

We developed 7 subjective profiles:

- a) profile card: online access to the health medicine;
- b) profile card: introduction to the genetic test;
- c) profile card: personal and family medical history;
- d) profile card: nutritional;
- e) profile card: physical activity;
- f) profile card: couple relationship;
- g) profile card: psychodynamics and stress management.

Objective biomolecular assessment

2.1. Predictive tests: genomics

The fruitful scientific and clinical collaboration between FlyLife (Milan), the *Asper Biotech Laboratory* (Tallinn), the *Institute of Medical Genetics* (Tallinn University) and *Locorotondo Labs* (Palermo) began back in 2004. Since then, it has achieved great results and has provided a priceless heritage, in spite of the shortage of funds and thanks to the commitment of many contributors.

2.1.1. “Genorama”

Genorama laboratory equipment was originally produced by Asper Biotech and was further developed by FlyLife, thus providing extremely precise and reliable microarrays.

The “Biochip Platform” was born thanks to the skills of the different groups that joined forces and supplied a wide range of polymorphisms associated with all the fields that define our state of health.

The interpretative “Report” is the real FlyLife’s identity card.

Thanks to this equipment, it is now possible to offer the screening of both a single disease (for example, Alzheimer’s disease) and an entire system (for example, the cardiovascular system).

2.1.1.1. The revolution of polymorphisms (SNPs)

«The only element that cannot lie about our state of health is our body».

2.1.1.2. The uses of DNA analysis

Thanks to DNA analysis, we can unmistakably identify the information contained in our genetic material. As a consequence, we are provided with a clear picture of the health of our cells and with a prediction of the risks we may incur in the future. Thanks to this assessment, the doctor can immediately intervene and prevent the risk.

In all likelihood, we will be able to analyze RNA as well in the near future. Thanks to RNA analysis and proteomics, the concept of early cancer detection will become out of date, insofar as cancer-causing molecular mechanisms will be identified, prevented and/or blocked.

2.1.1.3. How does a genetic test work?

The genetic test is neither invasive nor painful. It is easily carried out and consists of 3 phases:

- a) the applicant's activation procedure;
- b) the medical history questionnaire;
- c) the taking of a saliva sample by means of a buccal swab and shipping of the sample itself.

2.1.1.4. Activation procedure

Before undergoing the test, the applicant must follow the online procedure available on our platform.

The procedure is simple and intuitive. The applicant can get further information thanks to our kit.

Estimated time: 5 minutes.

2.1.1.5. Medical history questionnaire

Genetic tests are clinical products. It is important to assess the client's medical history in order to better manage and support their results.

In order to do that, the client is asked to fill in an online questionnaire concerning his/her medical history. It consists of simple

questions about the client's lifestyle and present and/or past pathologies.

Estimated time: 10 minutes.

2.1.1.6. Taking of a saliva sample by means of a buccal swab

Our kit includes everything necessary to take a saliva sample and ship it to our laboratories for its genetic analysis. The kit is designed to preserve the integrity of the biological sample.

The client can easily take the saliva sample by following the detailed instructions included in the kit.

The swab must be packaged according to the shipping procedure, put in the pre-stamped envelope and shipped to the specified FlyLife laboratory.

Estimated time: 2 minutes.

2.2. How the FlyAsper biochip was born and developed

Asper Biotec has been developing genetic tests based on DNA-microarray technology since 1999. Its scientific and laboratory team developed hundreds of DNA tests including thousands of genetic variations associated with both rare and widespread disorders.

The development of new DNA tests starts from the analysis of a wide amount of information concerning the genetic variations to be tested. The FlyChip microarray facility requires the selection of genetic variations whose names are internationally coded. They are called "rs numbers" and are organized in specifically designed databases. Asper Biotec bases its tests on these databases.

Bioinformatics is essential to develop new microarrays. It is able to draw small artificial DNA fragments called "oligonucleotides" or "primers". The drawing consists of a number of steps that guarantee the uniqueness of the nucleotide and the reliability of the biochip. Since the length of an oligonucleotide sequence corresponds to 25 bases, similar DNA fragments are likely to appear in other chromosomal regions. As a consequence, the signal produced by the microchip may not correspond to the marker we are looking for. Therefore, the clinical report may be incorrect. Asper Biotec has been developing

state-of-the-art softwares for the last 10 years in order to avoid the risk of analyzing aspecific oligonucleotides.

The buccal DNA collector:

- Handle with support (please write your name and your kit identification number in the designated area);
- Collection Paper;
- Sliding Cover.

Please read and follow instructions.

The sample should be self-collected to avoid any possible contamination.

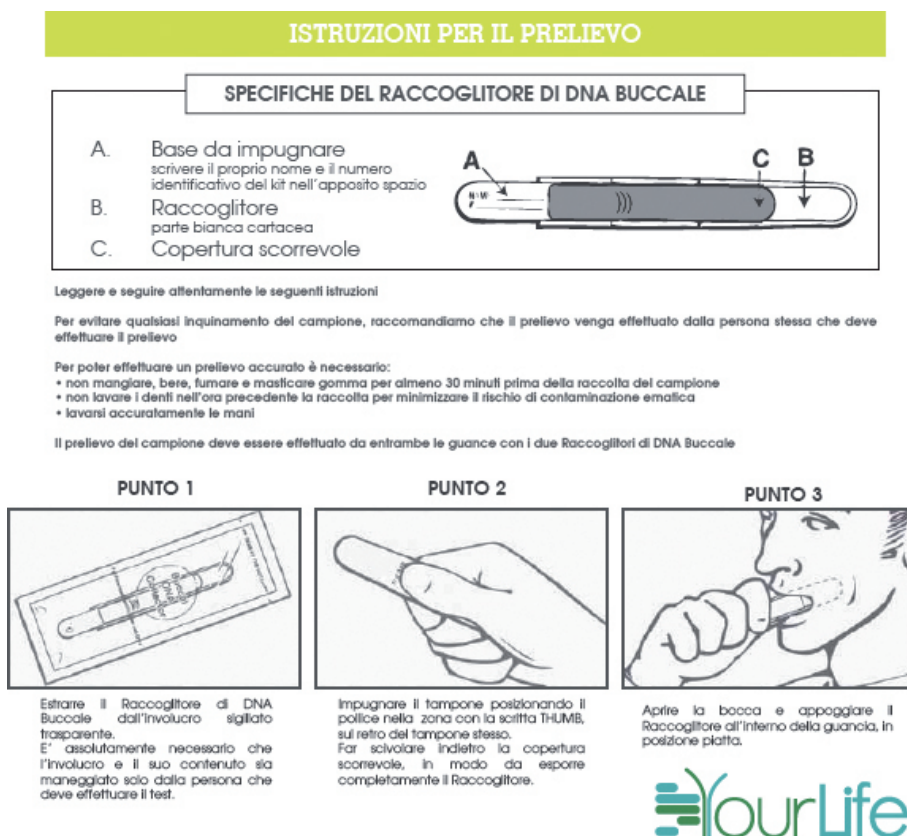


Figure 2.1. Describes how the saliva sample should be taken and shipped.

The subject should:

- not eat, drink, smoke or chew gum in the 30 minutes prior to providing the sample;
- not brush his/her teeth in the 60 minutes prior to providing the sample;
- wash his/her hands carefully.

The sample collection procedure must be performed from both the cheeks.

- *Step 1*: remove the buccal DNA collector from the pouch, holding the Handle at the base. The collector must be handled only by the subject who is self-collecting the sample.
- *Step 2*: hold the buccal DNA collector and put the thumb on the area marked “thumb” on the back of the collector. Move the Sliding Cover back to fully expose the Collection Paper.
- *Step 3*: open your mouth and place the white Collection Paper side flat against inside of cheek.

Over 1,000 oligonucleotides have been developed for the FlyChip so far and the process is still in progress. Every genetic variation will be identified by the APEX microarray by means of two different primers.



Figure 2.2. Instructions for the taking of the saliva sample.

Two DNA fragments are simultaneously identified in a single reaction, thus improving the specificity and effectiveness of this technology. Primers are supplied by extremely reliable producers.

In the meantime, Asper Biotech's chemists prepare microarray glass slides covered with "silane", a complex inorganic compound that enables the transfer of large artificial DNA fragments. When the FlyChip gets to the laboratory, DNA oligonucleotides are "spotted" onto the array. Every specific oligonucleotide associated with a tested genetic variation is transferred, thanks to robot technology, onto a default site of the glass slide. The FlyChip microarray is ready to be optimized in laboratory.

Then the laboratory prepares a special mixture necessary to the polymerase chain reaction. This chemical procedure generates thousands to millions of copies of a particular DNA sequence containing the tested genetic variations and makes them visible on the microarray. Even though this technology is currently well-established, it requires time, experience and attention.

- Step 4: Press Collection Paper against inside of cheek and drag it firmly towards lips and out of mouth (this motion is similar to the "popping" of the cheek with a finger that children do).
- Step 5: repeat this action 7 more times. It is important to press Collection Paper flat against cheek and drag it across and bulge the cheek out during collection. DO NOT rub the collector back and forth against cheek. It is not a toothbrush.
- Step 6: push the Sliding Cover forward towards the tip of the collector, covering the Collection Paper. Repeat the procedure with the second collector in the kit. Follow instructions from step 1 to step 6 with the other cheek.

After completing the polymerase chain reaction, the central part of DNA hybridization technology and of primer lengthening is tested and optimized. A set of FlyChip microarrays is produced while the samples are increased through the polymerase chain reaction. The samples are checked many times during the procedure.

Once the laboratory director confirms that the operating protocol has been observed, a set of DNA samples undergo validation and further quality control. Ten anonymous DNA samples are chosen at

random and are analyzed many times. The results are also analyzed as “blind samples” (the laboratory technicians don’t know that the sample has already been analyzed).

Thanks to this procedure, the performance of the test is assessed through the results of different validation studies.

2.2.1. *The methodology of gene selection*

All genetic tests are based on the selection of the genes that must be analyzed in order to identify which polymorphism is present. Diseases (except for rare hereditary diseases) are not caused by a single gene, but by many of them. Hence, the golden rule of genomics: the more genes are analyzed, the closer we get to the risk definition (Fig. 2.3). Since we currently do not know the entire set of genes associated with a disease, we rely on an approximation formula based on specific algorithms. In other words, the reliability of a genomic test depends on the selection of the genes to be tested, on the interpretation algorithm and on the quality of the laboratory.

Just like any other laboratory that performs genomic tests, our team selected the genes of the FlyChip from the huge American database MED PATH (Fig. 2.4).

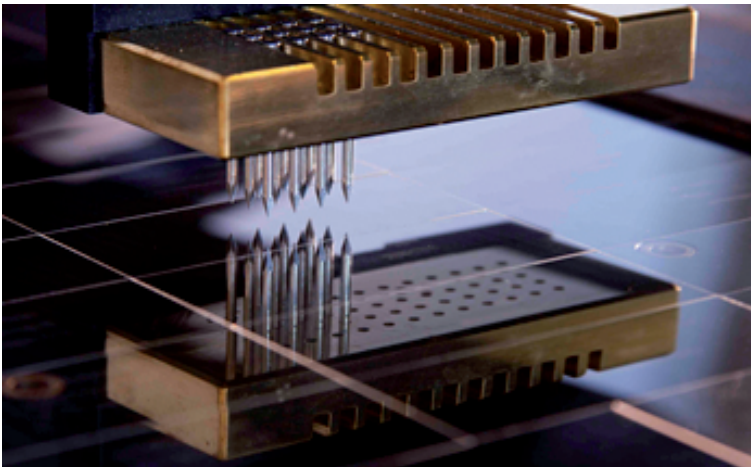


Figure 2.3. Microarray glass slides are “spotted” by means of high-definition robot technology.

Gene selection is based on the permanent commitment of our medical staff and began in 2004 starting from the scientific evidence acquired from international medical journals. As a consequence, our team selected those polymorphisms that are more often related, from a statistic and genetic point of view, to a specific disease. They only considered the polymorphisms associated with a particular disease in Euro–Caucasian populations.

Since gene and protein expression changes depending on the ethnic groups and genetic research has focused on North American, European and Asian populations so far, it will take some more years before other ethnic groups are tested.

There are 2,000 polymorphisms associated with chronic–degenerative diseases: our team selected 1,000 of them. We are by no means inferior to the renowned American genomic centers.

In the following paragraphs we will sum up the processing of the Fay Biochip.



Figure 2.4. FlyChip optimization.