

SUPPLEMENT I

USZ-ARVC GENETIC TEST PATIENT INFORMATION BROCHURE AND INFORMED CONSENT

1. What is ARVC?

ARVC stands for “**A**rrhythmogenic **R**ight **V**entricular **C**ardiomyopathy”, an inherited heart-muscle disease that is a cause of sudden death in young people and athletes. ARVC accounts for up to 20% of young people who experience sudden cardiac death. The disease was described for the first time in 1978 and is characterized by either massive or partial progressive replacement of heart muscle by fatty or fibro-fatty tissue. This infiltration provides a substrate for electrical instability and leads to dangerous heart rhythm disturbances and/or heart enlargement and insufficiency. The prevalence of the disease in the general population has been estimated to range from 1 in 2000 to 1 in 10 000. Eighty percent of ARVC cases are diagnosed in patients less than 40 years of age.

2. What is the USZ-ARVC Genetic Test?

The human genetic heritage is present in the nucleus of every cell of the body. Genes are the units of heredity and consist of DNA. Everyone is born with a unique set of genes. Small defects in particular genes may cause a disease or birth defect. A genetic test is any analysis used to look at a person’s genetic information. Genetic test allow determining whether a person is a carrier of a mutation, which may be inherited and associated with disease in his or her offspring. To date, near 260 putative ARVC mutations distributed across 10 genes, have been described (<http://www.arvcdatabase.info/Default.aspx>). Nevertheless, 90% localize to only 5 genes: *DSC2*, *DSG2*, *DSP*, *JUP* and *PKP2*. The ARVC genetic test performed at the University Hospital of Zurich (USZ) analyze the above 5 genes.

3. What are the limitations of the USZ-ARVC Genetic Test?

Despite the important knowledge generated in the last 2 decades, the comprehensive mutational analysis of all known ARVC genes is able to detect genetic abnormalities in only 55% of the ARVC cases. A negative test only indicates that the genetic mechanism implicated in that person is still unknown, further medical research is needed to understand the genetic basis of the disease. Moreover, the possibility of missing an existing variant with the USZ-ARVC genetic test technique is estimated to be 0.5-2%. Detection of large genomic deletions/duplications is not part of this test. The test will not detect errors involved in the DNA “read-out”, known as RNA transcription or processing.

4. What are the benefits of the USZ-ARVC Genetic Test?

- A positive test is considered a major diagnostic criteria for ARVC. Sometimes the disease is subtle and the clinician does not have enough elements to make a diagnosis and start appropriate treatment. In this context, the ARVC genetic test is important for the diagnosis of ARVC.
- Having the knowledge of an ARVC mutation can empower a person and family members to make important life planning decisions.
- Detecting the ARVC mutation in one individual facilitates the identification of other asymptomatic family members at risk, which can get the benefit of early medical attention and prevention of sudden cardiac death. All first-degree relatives of an individual with an ARVC gene mutation have up to 50% risk of harboring the same mutation.

5. What are the risks of the USZ-ARVC Genetic Test?

- The physical risk of the genetic test is minimal. Usually not more than providing a blood sample (5-10ml) for DNA extraction. If in your particular case other type of tissue is needed for the genetic analysis, your physician will explain you the particular risk of the procedure.
- The decision to have a genetic testing can be stressful. You may have emotional reactions to learning that you do-or does not carry a gene change for ARVC. For these reasons, meeting with therapist and geneticist may be indicated.
- A positive test result can affect family relationships. A person who decides to have genetic testing needs to consider whether to tell other family members. The result for one family member can disclose the information about the genetic make-up of other relatives, even if they have not been tested.

6. What if I refuse to have the USZ-ARVC Genetic Test performed?

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You have the right to refuse to have the ARVC genetic test performed. Your medical treatment will not be jeopardized whatever decisions you or your family make.

7. What do the results of the ARVC-Genetic Test mean?

Sometimes the genetic test does not provide a “yes” or “no” answer. Classification of each detected variant is based on the likelihood of being associated to the disease. The USZ-ARVC genetic test will classify the genetic variants detected according the following:

- **Genetic Variant Class A:** Are deleterious and probable deleterious mutations, usually reported in the scientific literature as disease causing or mutations that produce an important change in the protein, expected to cause the disease. Typically these variants are absent from a healthy normal population.
- **Genetic Variant Class B:** Are variants of uncertain significance, means that there is not enough scientific evidence that this variant is a disease causing. Typically these variants are absent from a healthy control population.
- **Genetic Variant Class C:** Polymorphisms. These are variants not generally expected to cause disease. Typically these variants are common in a healthy control population.

This classification has been developed based on the scientific literature and is continuously updated. A change in the interpretation of a reported variant is possible due to the constant generation of novel scientific evidence.

8. What will happen with my sample after the ARVC-Genetic Test is completed?

After the genetic test is completed we will store your sample/DNA for 1 year, only for the purpose of verification of our test results. You will indicate at the end of this consent form if you want your sample to be destroyed after the genetic test and verification process is completed or if you allow the researchers to use your sample to study other genetic mechanism potentially implicated in ARVC. If you want your sample to be used for research purposes, you will also be able to decide if you want to be informed about the results or not. Your participation in genetic research studies is voluntary and can be withdraw at any time without any consequences in your medical treatment.

9. Who has access to my sample and information from the test?

The ARVC genetic test is handled in a confidential manner, like other personal health information. The person collecting your sample, and people in the laboratory performing the test, will handle your sample. Your medical record and test results are confidential. The results of the genetic test will be available upon request for you or for the parent/legal representative when applicable.

10. What is the cost of the USZ-ARVC Genetic Test?

The ARVC genetic test performed at the USZ includes the analysis of 5 ARVC genes (*DSC2*, *DSG2*, *DSP*, *JUP* and *PKP2*) and cost CHF 950. If one specific mutation needs to be confirmed in a relative or family member, the cost will be CHF 350 and the screening will be limited to that specific mutation only. The coverage of the genetic test by insurance companies is variable, we recommend you to ask your health insurance if they cover the ARVC genetic test. Currently, the USZ-ARVC genetic test is in the process of being officially accredited, patients/samples scanned during the accreditation process will be waived of the cost mentioned above.

11. How long does it take to have the USZ-ARVC Genetic Test results?

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The results of the genetic analysis of the 5 ARVC genes (*DSC2*, *DSG2*, *DSP*, *JUP* and *PKP2*) performed in the USZ-ARVC genetic test are on average ready to be reported in 3 months and usually no longer than 6 months. Since the ARVC genetic testing developed at the USZ is being accredited, results will not be released until the accreditation processed is completed.

12. Genetic Counseling Remarks

In order to be aware of the aims, consequences and limitations of genetic testing, adequate genetic counseling by a trained professional is highly recommended. Genetic tests have to be ordered by physicians or by legally supervised doctors. Those who order a genetic test have to make sure that adequate genetic counselling is provided. Genetic testing, like any other diagnostic procedure, is voluntary and requires formal consent. You are invited to take the time to ask all the questions you might have as well as to make an independent personal decision. It may be appropriate to reconsider your decision and ask for a second appointment.

After reading this brochure and discussing with your physician, the following aspects should be covered and clear to you before you decide for or against the USZ-ARVC genetic test:

- The **major medical facts** including the diagnosis, prognosis and ways of prevention and treatment of ARVC
- The **genetic facts** involved including risks for other family members.
- The probability that the test will give a correct result or prediction, or indeterminate or unexpected findings.
- The risk of receiving an **unfavorable test** result and the **possible consequences** for yourself and your family.
- **Alternatives** to genetic testing.
- **Consent:** If the person being tested is under age or unable to reason, the legal substitute has to give informed consent. This consent can be withdrawn at any time.
- Your right **not to know:** each person has the right to deny information about his/her genetic makeup.
- You're right to **refuse** the test.
- Potential benefits and disadvantages, including **unsettled questions** of privacy protection dealing with insurances, banks or employers.
- Your care will **not be jeopardized** whatever decision you and your family make.
- Possible use of your tissue sample after testing: kept for reanalysis upon request, biobanking (storage), use for medical research or destroyed.
- Information about the **costs** and whether covered by health insurance or not.

Legal Framework

Federal law on human genetic analyses (LAGH – GUMG, in effect since 01.04.2007).

Has to be filled in by the person tested (in capital letters)!

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First Name _____ **Last Name** _____

Date of Birth ____/____/____

"I confirm that I have received genetic counseling according to the federal law on human genetic analysis (GUMG) and that enough time for questions has been provided"

I hereby agree to have the USZ-ARVC Genetic Test done. Yes No

Please send me a copy of the test results Yes No

My decision for the sample after the test is completed:

My sample can be used for medical research, and I want to be informed about the results (non anonymous)

My sample can be used for medical research, and I don't want to be informed about the results (anonymous)

My sample must be discarded

Other: _____

Signature _____ **Place and Date** _____
(Parent, legal representative when applicable)

Information and signature of the physician ordering the test

(Without the signature and stamp, the genetic test will not be performed)

Name of the physician: _____

Hospital/ specialty: _____ Tel./ fax/ pager: _____

Date of material sampling: _____

Type of material: EDTA- blood other material: _____ Amount: _____

Signature _____ Place, date: _____

Physicians stamp:

Copy to (e.g. general physician, staff physician): _____