User Manual for Agile 3+ V1

E506M001.1 – Agile 3+ v1.0 – January 2020

EN

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1. Purpose of the user manual

The present User Manual has no contractual value whatsoever and under no circumstances may Echosens be held responsible on the basis of the information contained in the present manual.

The present User Manual details the information required for the use of Agile 3+ computation.

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Any information or modification requests pertaining to this manual should be sent to: Echosens, 6 rue Ferrus, 75014 PARIS, France or support-it@echosens.com.

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2. Indications

Intended Use

Agile 3+ is an algorithm using liver stiffness measurement, clinical and laboratory parameters intended to compute a probability of advanced fibrosis in patients with suspicion of Non Alcoholic Fatty Liver Disease to help the physician identify those patients.

Indication for use

Agile 3+ is indicated in patients with suspicion of Non Alcoholic Fatty Liver Disease to identify advanced fibrosis defined as a fibrosis stage superior or equal to F3 according NASH CRN scoring system. It may be used as an aid to diagnosis and monitoring of patient with Non Alcoholic Fatty Liver Disease.

Precautions for use

The following circumstances may affect the results obtained and therefore may affect the interpretation of Agile 3+ result:

- Pregnancy
- Patients under 18 years of age
- Other chronic or acute liver disease than NAFLD
- Liver transplant patients
- Cardiac failure and/or significant vascular disease
- Confirmed diagnosis of active malignancy or other terminal disease
- Use of treatment inducing liver injury

To get a reliable result:

- LSM should come from an examination performed with a FibroScan device
- LSM and blood collection for AST, ALT and PLT measurements should be performed within 31 days.

Target Population

Agile 3+ is indicated for adult patients with suspicion of NAFLD.

Intended User

Intended users are clinicians dealing with patients suspected of liver diseases.

Intended Environment

Agile 3+ is accessible through devices connected to the internet using dedicated services. Users shall authenticate and confirm his/her status and abilities to use Agile 3+.

3. Classification

Agile 3+ is Medical Device (class I) according to directive 93/42/EEC.

4. Performance characteristics

Claimed performances characteristics

Agile 3+ compute a value between 0 and 1, if all input parameters have been entered with the appropriate units.

Specified clinical benefits

Non-invasive aid to diagnosis and monitoring of advanced fibrosis in patients with Non Alcoholic Fatty Liver Disease.

Clinical results summary

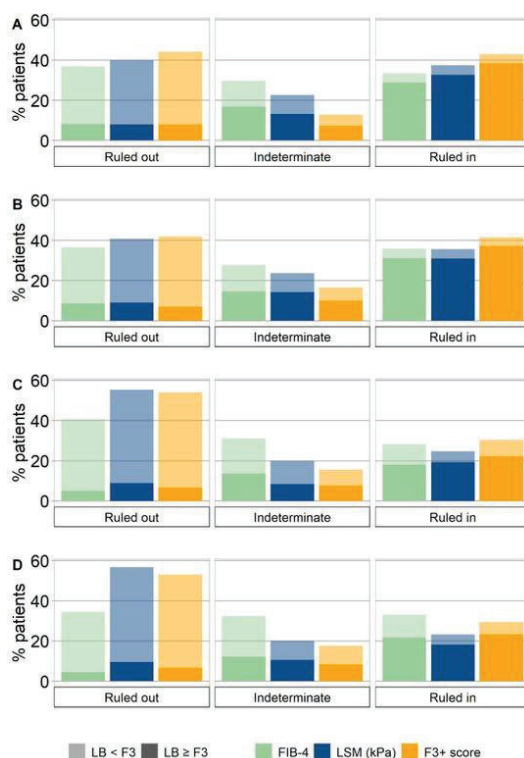| Data sets (N, Prevalence of F≥3 = %)	F3 Score / Agile 3+ AUC [95%CI]	LSM AUC [95%CI]	FIB-4 AUC [95%CI]
Internal validation (700, Prevalence = 54%)	0.90 [0.88-0.92]	0.85 [0.82-0.88]	0.84 [0.81-0.86]
External validation #1 (585, Prevalence = 37%)	0.86 [0.84-0.89]	0.83 [0.80-0.80]	0.78 [0.74-0.82]
External validation #2 (1042, Prevalence = 38%)	0.87	0.84	0.78

Table 1: Agile 3+Clinical Performances: AUCs

Figure 1 : Percentage of patients in rule out (<85% Se threshold), indeterminate and rule in zones (≥90% Sp threshold) for the diagnosis of advanced fibrosis with FIB-4, LSM and F3 score

5. Technical recommendations for FibroScan® procedure

The measurement of liver stiffness (E) shall be done by an operator trained and certified by Echosens or its local representative according to the recommendations of Echosens with a probe fitted to the morphology of the patients as described in the FibroScan® user guide.

The FibroScan® examination results should fulfill reliability criteria defined in the publication entitled "Determination of reliability criteria for liver stiffness evaluation by transient elastography" by Boursier J, Zarski JP, de Ledinghen V, Rousselet MC, Sturm N, Lebail B, Fouchard-Hubert I, Gallois Y, Oberti F, Bertrais S, Cales P and the Multicentric Group from ANRS/HC/EP23 FIBROSTAR St published in Hepatology in 2013 volume 57(3) page 1182-1191.

6. User registration for Agile 3+ access

Downloading and sign in

myFibroScan application can be used on iOS and Android platforms. It is available on both Apple store and Google play store. Once it has been downloaded, anyone can launch the application but he/she has to be registered to access Echosens services.

The screen aside appears. The application is available both in French and English. However, by default, this page language is based on the phone language.

If the user is already registered, he can connect himself/herself by entering his/her login and password and clicking on "Sign In" button. If not, the user should create an account by clicking on "Sign Up" button.

Once signed-in, unless he/she specifically logs out from the application, the user will be automatically logged-in and will not have to enter his credentials again.

Figure 2: Sign In screen

Registration

To access Agile 3+, any user has to create an account on Echosens Cloud services by clicking on "Sign Up". He/she then accesses to the following screens:

Figure 3: Account creation on Echosens Cloud Services

Any field with a star is required. Language, specialty, type of institution and country are to be chosen in a picklist. Password shall fit the following rules to be acceptable:
- composed of alphanumeric characters
- contain at least 8 characters

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- contain at least one digit
- contain at least one uppercase
- contain at least one lowercase

All conditions have to be acknowledged by checking the checkbox except the last one before the user can confirm his/her registration.

General Conditions for Use are available on Echosens website and are accessible by clicking on the link.

Then, the user can sign up. If all mandatory fields are correctly filled, a message will confirm his/her account creation and display the next instructions. Otherwise, an error message will appear to guide the user.

An automatic message will be sent to the user mailbox to confirm his/her email address. The user has to click on the confirmation link before being able to login into the application (account activation).

7. Agile 3+ use cases

Using myFibroScan accessory

Home page

Once logged-in, the user access to the home page screen (figure 3).

- Agile 3+is available under the "Score" menu

Inputs screen

By clicking on the "Agile 3+ " block, the user accesses to the Agile 3+ input screen (figure 4).

The user can fill E (Stiffness) values manually or by scanning a QR code printed on a FibroScan examination report.
The other input parameters shall be entered manually.

Invalid values will be notified to the user. He will not be able to submit its computation with out of range values of bad/missing units.

The user has to confirm that:
- No more than 1 months separates FibroScan examination and blood sampling
- the physician is aware of precautions for use related to Agile 3+ score computation

The user can access to:
- This user guide by clicking on "Learn more"
- Agile 3+ formula by clicking on publication

Then, the user can submit his/her computation or go

back to the home page by clicking on the pictogram.

Results screen

After submission, the user accesses to the results screen. He/She can consult the input parameters he/she submitted and the associated result. If he/she wants to update one of these values, the user can come back to the inputs screen by clicking on the pictogram.

Again, the user can access to:
- this user guide by clicking on "Learn more"
- Agile 3+ formula by clicking on publication

From here, he can generate the corresponding report by clicking on "Create a report" or go back to the home page by clicking on the pictogram.

Report creation

To generate a report, the user has to enter personal patient data. Several options are possible:
- If E value has been scanned from a FibroScan examination report, then the corresponding patient information are automatically filled and the user only needs to confirm the statement: the patient is aware of data processing before being able to generate the report

- If not, the user can re-use data previously entered by selecting a patient from the patient list and confirm the statement

Or he/she can create a new patient file. It will be locally stored on the phone and will be visible in the patient list for future use. Fields with a red star are mandatory.

Once done, the user can submit the data or go back to the home page by clicking on the pictogram.

Once submitted, the user has to fill or select FibroScan examination date and blood collection date (figure 7).

Even if the time elapsed between these two dates is longer than the threshold mentioned in the Agile 3+ input specifications, the report will be generated. However, the Agile 3+ result will not be displayed as it does not meet the specific indications agreed by the user to use the Agile 3+ computation module.

Once done, the user can click on Submit button. The report is generated, downloaded on the phone and can be open by any PDF reader available on the device. He/She can go back to the home page by clicking on the ⌂ pictogram.
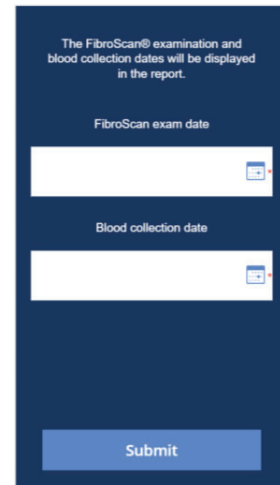

Figure 4: Examinations dates

Using Echosens API

Users can performs direct API call without using myFibroScan interface to perform Agile 3+ computations.
- They won't be allowed to generate report
- The user shall have been signed-up to ECS using myFibroScan interface beforehand.

Authentication via API

To access Agile 3+ features, users shall authenticated via API request (token authentication)

this is a POST request with the following attributes.

url

https://myfibroscan-eu-west-1.echosens.cloud/authorize

header

```
{
        "content-type": "application/json; charset=utf-8",
        "Accept": "application/json"
}
```

json

```
{
        "userName": your_username,
        "pwd":  your_password
}
```

your access token is in the "Authorization" attribute of a successful request. You should add it to the header of all the

following requests, in the "Authorization" attribute, prefixed by "Bearer " as explained below.

Score computation via API

Once the authentication token is obtained, the user can perform computation request as follow:

This is a POST request with the following attributes.

url

https://myfibroscan-eu-west-1.echosens.cloud/score-f3/apis/compute

header

```
{
        "content-type": "application/json; charset=utf-8",
        "Accept": "application/json"
        "Authorization": "Bearer your_authentication_token"
}
```

json

```
{
        "lsm": {
                "value": 9.0,
                "unit": "kPa"
        },
        "ast": {
                "value": 20,
                "unit": "U/L"
        },
        "alt": {
                        "value": 20,
                "unit": "U/L"
        },
        "plt": {
                "value": 150,
                "unit": "10*9/L"
        },
        "age": {
                "value": 41,
                "unit": "a"
        },
        "diabete": false,
        "gender": "Female",
        "bsDate": "YYYY-mm-dd",
        "fsDate": "YYYY-mm-dd",
        "precAndCIOk": true,
        "disclaimerOK": true,
        "country": "France"
}
```

A successful request will return a json structure as output

```
{
        "results": {
                "score": the_numerix_result,
                "image": the_enpred_result_image
        },
        "inputs": the_inputs_used_for_computation
}
```

8. Symbols on the device

Agile™ 3+   Agile 3+ device

CE   CE marking affixed by Echosens in May 2021

MD   Medical Device

   Manufacturer

Contact us

The user can contact Echosens by clicking on the Contact us pictogram. It will redirect him/her towards the support platform in which he/she will be able to fill a request form.

About

By clicking on the About pictogram, the user can consult general information regarding Echosens, myFibroScan, trademarks and patents.

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Echosens
6 rue Ferrus
75014 Paris
FRANCE
+33 1 44 82 78 50
www.echosens.com
support-it@echosens.com