REDACTION Nom : C. Jacquelin	VERIFICATION et APPROBATION Nom : P.-J. Touboul Date :
DIFFUSION IntimaMedia.com DHF IntimaMedia.com DMR (approving documents)	

Historique des MODIFICATIONS

Date	Indice	Nature de la modification
12/02/10	A	Création avec prise en compte des exigences de la norme CEI 62304.
22/02/10	B	Révision, édition, A. Puech Bournonville.
24/02/10	C	Révision Pierre-Jean Touboul.
19/05/10	D	Mise à jour des risques ; C. Jacquelin.
09/05/11	E	Mise à jour pour Etude TST.
20/07/11	F	Mise à jour pour la version 2.0.0.
12/05/12	G	Seconde mise à jour pour la version 2.0.0., Suppression des spécifications relatives à la version 1, modification des spécifications : 3.1, 3.2, 3.4, 3.5, 3.6, 3.7, 3.11, 3.12, 3.14, puis renumérotation.
12/11/12	H	Mise à jour suite réunion du12/11/2012.
22/05/13	I	Mise à jour pour Revue E1 à E3 du 22/05/13

Historique des MODIFICATIONS

Date	Version logiciel	Modification Mineure / majeure	Elément de configuration modifié	Source*
20/07/11	2.0.0	Majeure	Interface, Base de données.	

* référence bug et/ou RC

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1. 0. SCOPE

This document describes the detailed design of the Intimamedia.com software. It provides:

- 1. Description of the system level with a description of the purpose, functionalities, and interface of the software replying to the IEC 62304 standard, § 5.2
- 2. Detailed SDD

This document, after its approval, is an output of the software development. It describes how the requirements will be implemented for IntimaMedia.com software. IntimaMedia.com software design fulfils the software requirements specified in the Software Requirements Specification document.

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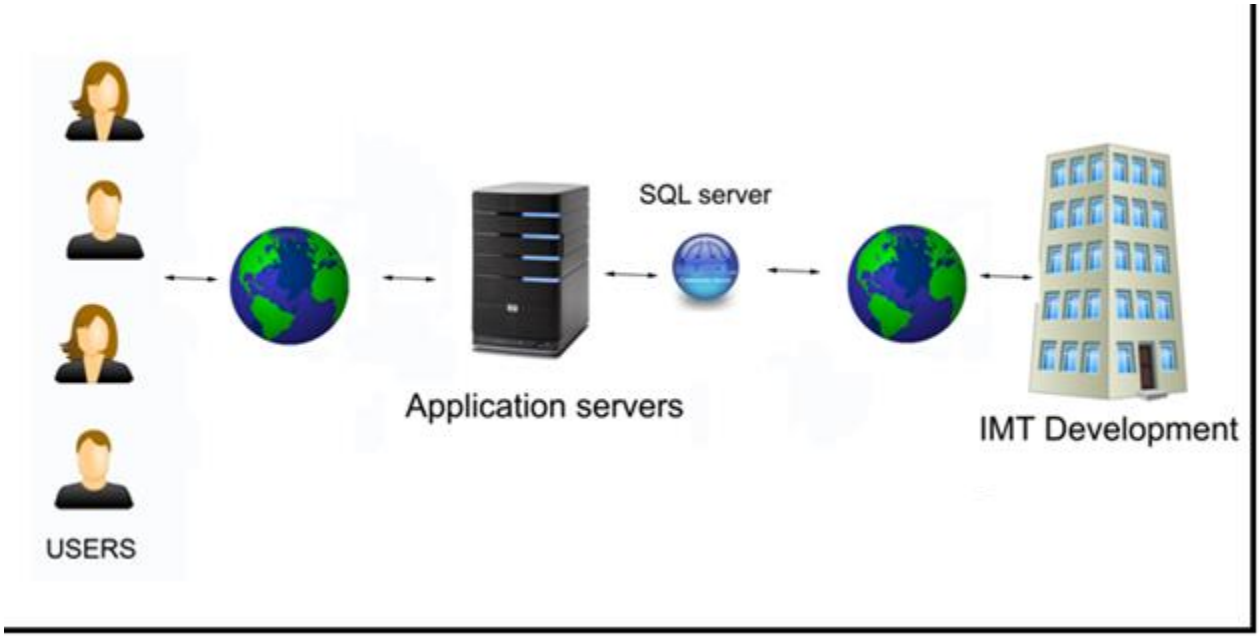
2. ARCHITECTURE OVERVIEW

There is below a description of the architecture of the application. Users of the application are located anywhere around the world. They are connected to the application through the internet network. The Flex application is located on a Server. When they get connected, the application is automatically downloaded to the user's PC. The application data are located on the application Server (in an external web hosting company). The application which is now on the user's PC is reading and writing data in the database on the server, and reading or writing images on the server. IMT development team sends the new version of the application to the application server.



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3. DETAILED SDD

This section contains the detailed description.

3.1 Web Application: General

The IMT logo colours are based on white, grey and red. The logo of the company is:

For IntimaMedia.com colours, we have kept the red point, and the white and grey. Below is the logo of IntimaMedia.com:

The application is optimized for 1440x900 screen size. You will find below results of statistics regarding screen resolution:

Screen resolution	PC-Laptop Market (2010)
1024 x 768	57%
800 x 600	17 %
1280 x 1024	16 %
1152 x 864	3 %
Unknown	3 %
1600 x 1200	0 %
640 x 480	0 %

Swf file of the application generated by Flex Builder cannot be read by search engines like Google (at this time). That's why we have included in the html start page some important keywords. This page in Html will be referenced by search engines like Google, Yahoo and others. Also, the site will be referenced.

On the html start page of the site we have include scripts from Google Analytics. Also, statistics of the web site will be available.

The release of a new version is invisible for the users. When a new version is ready, the IMT development team is sending the application to the web hosting server, and then users can use this new version when they get connected (after clearing the memory cache). This is one advantage of this application, users

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don't need to uninstall the software on their computer, and install the new version, as it is necessary for regular desktop software.

The application can be used by several users at the same time. Since a copy of the Swf file located on the server in downloaded on the user PC each time a user get connected. The computer power used is the one of the PC user mainly and depends on its internet connection.http://www.google.fr/intl/fr/options/

The Swf file generated by the application is interpreted by Flash Player, which is present on 97% of PC connected to the internet. The Flash Player is compatible with the entire web browser. Below is a table of Browser statistics in January 2010 (from www.w3schools.com). Note that Internet Explorer and Firefox are the most common browsers.

IE8	IE7	IE6	Firefox	Chrome	Safari	Opera
14.3%	11.7%	10.2%	46.3%	10.8%	3.7%	2.2%

The data of the application are stored in a SQL databases. There is one database for the Physician version, and one for each study of the clinical studies version.

The software is developed in Adobe Flash Builder 4.6, with the integration of the CairnGorm framework for a better code maintenance.

Covered Spécifications	1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 1.10

Associated Risk	N/A

Risk management:

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3.2 Graphical User Interface: General

The application starts with a home page in which the user can choose between the medical physician (MP) and the clinical study (CS) web application version. Capture of the home page showing the choice:

We notice that the user has to certify that he (she) is a medical physician to access to the MP version, or that he (she) is involved in a clinical study to access to the CS version.

The Graphical User Interface application doesn't contain any menu. The access to the different functions is provided by tabs.

Tabs for the Physician version:

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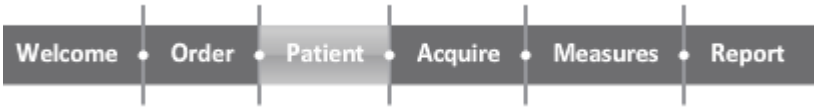


The application provides message boxes (called Toasters) for useful information to the user. Below is the message box when the user enters a wrong password:

At the top of the application, we can see:

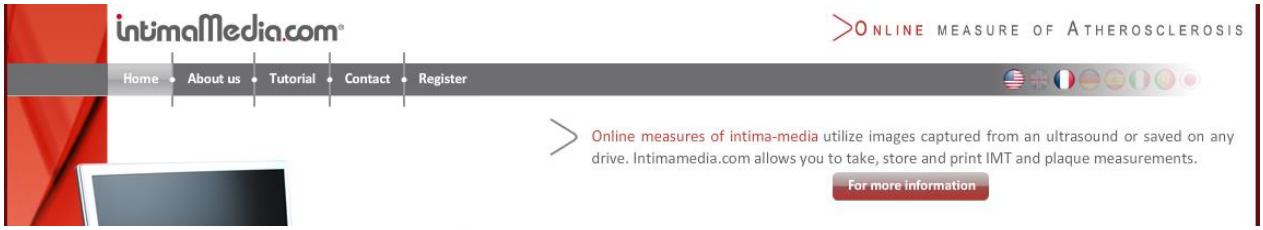
- Which user is connected?
- Flags for changing of the current application language.
- A button to logout of the session (once login).

Capture of the top line of the application:

At the top of the Home Website page, we can see:

- The IntimaMedia.com logo.
- The marketing signature.
- The Flags for changing the home Website language.

Capture of the top line of the home website:



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Covered Specifications	2.1, 2.2, 2.3, 2.4, 2.5

Associated Risk	N/A

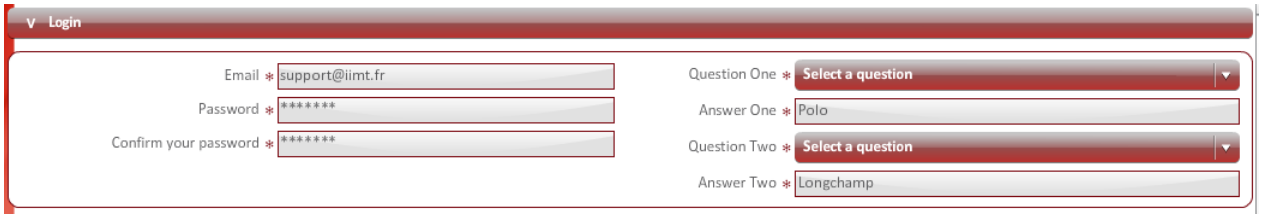
Risk management:

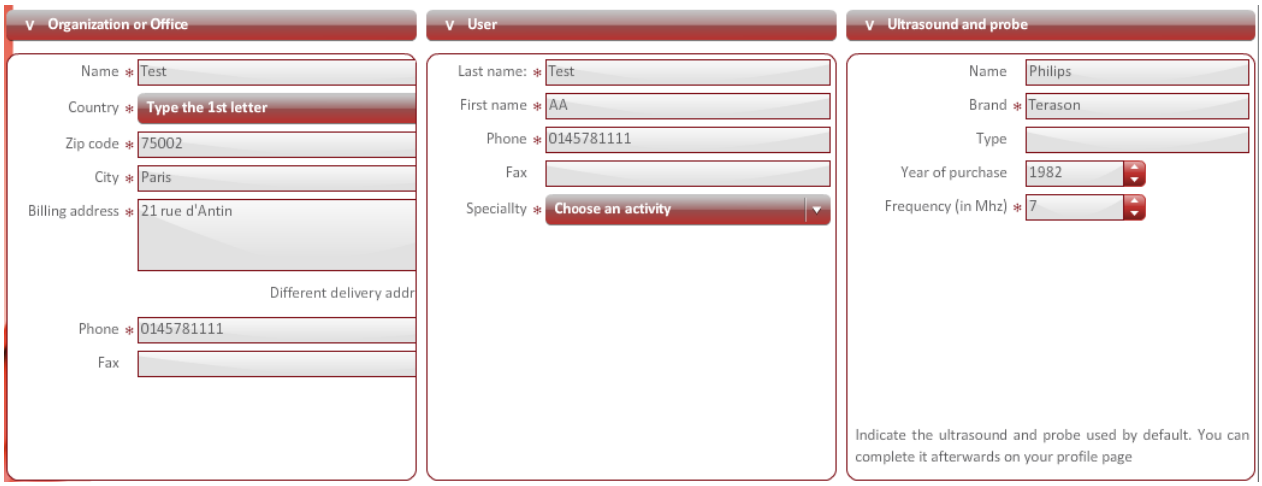
3.3 Graphical User Interface: Home Tab

When a new user registers, he will have to fill out a web based form with information on:

- The user Email and its password.
- The secret questions for the password recovery.
- The Center
- The Sonographer.
- The Ultrasound device.

Capture of the web based registration form:

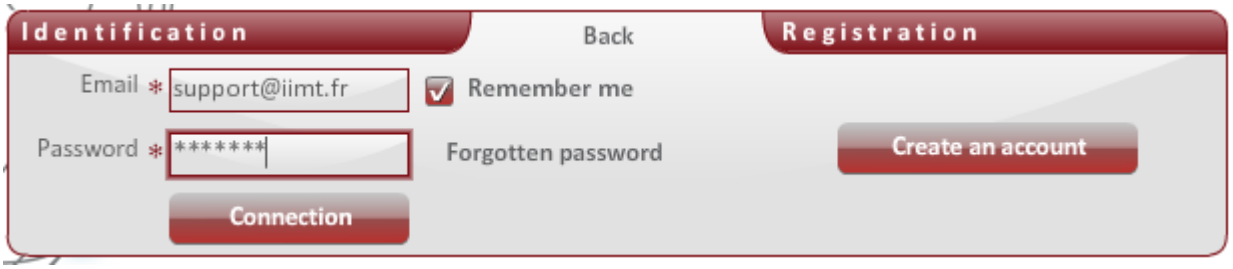




All the fields with a red star are required. Then he can register by clicking on the Registration, button. The data are written in the database and IMT Company receives an Email.

The user can access the application by entering its Email and Password.

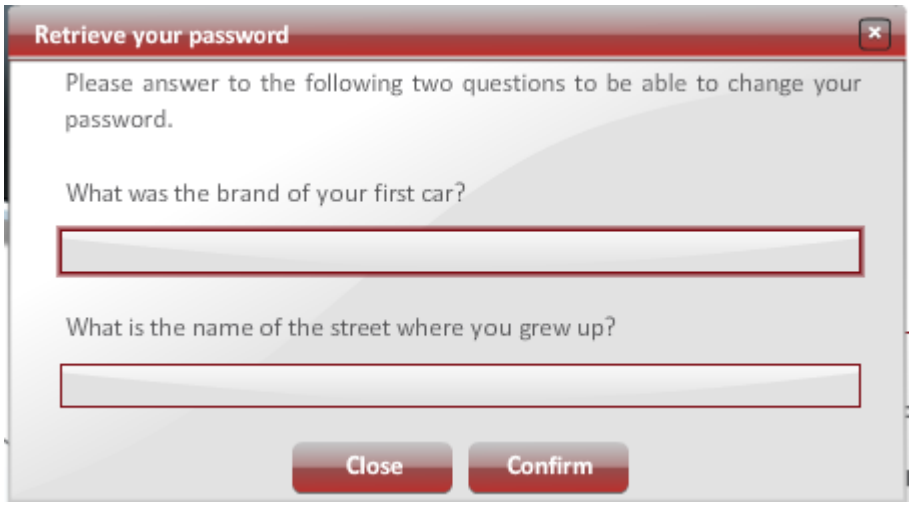
Capture of the user connection interface:



If the user loses its password, the application display on the screen, after he (she) had clicked on the button “Forgotten password” and answers to its own 2 secret questions.

.

Capture of the message box displayed when password has been lost



As long as the user doesn’t enter his (her) correct login and password, the other tabs are disabled and he (she) cannot access the application. The Home tab and Order tab are always enabled.

Capture of the top Tab menu in non registered or wrong password conditions

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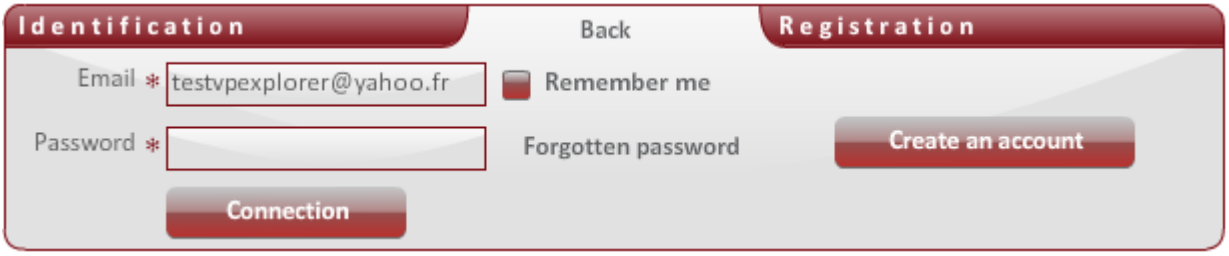
When a user connects for the second time from the same computer, his Email value is automatically displayed in the Login field as far as he had checked the Remember box during the last connexion. A cookie is used to store the user Email value on its computer.

Capture of the message box displayed for registered user



Spécification(s) couverte(s)	3.1, 3.2, 3.3, 3.4, 3.5

Associated risk	N/A

Risk management:

3.4 Graphical User Interface: Tutorial Tab

When the user is logged, tutorial videos are available to learn how to use the application. Tutorial topics are:

- Scale settings
- IMT Measure.
- Distance Measure.
- Surface Measure.

Covered Specifications	4.1

Associated Risk	N/A

Risk management:

3.5 Graphical User Interface: Patient Tab

For the medical physician (MP), the patient data are more detailed. They are related to:

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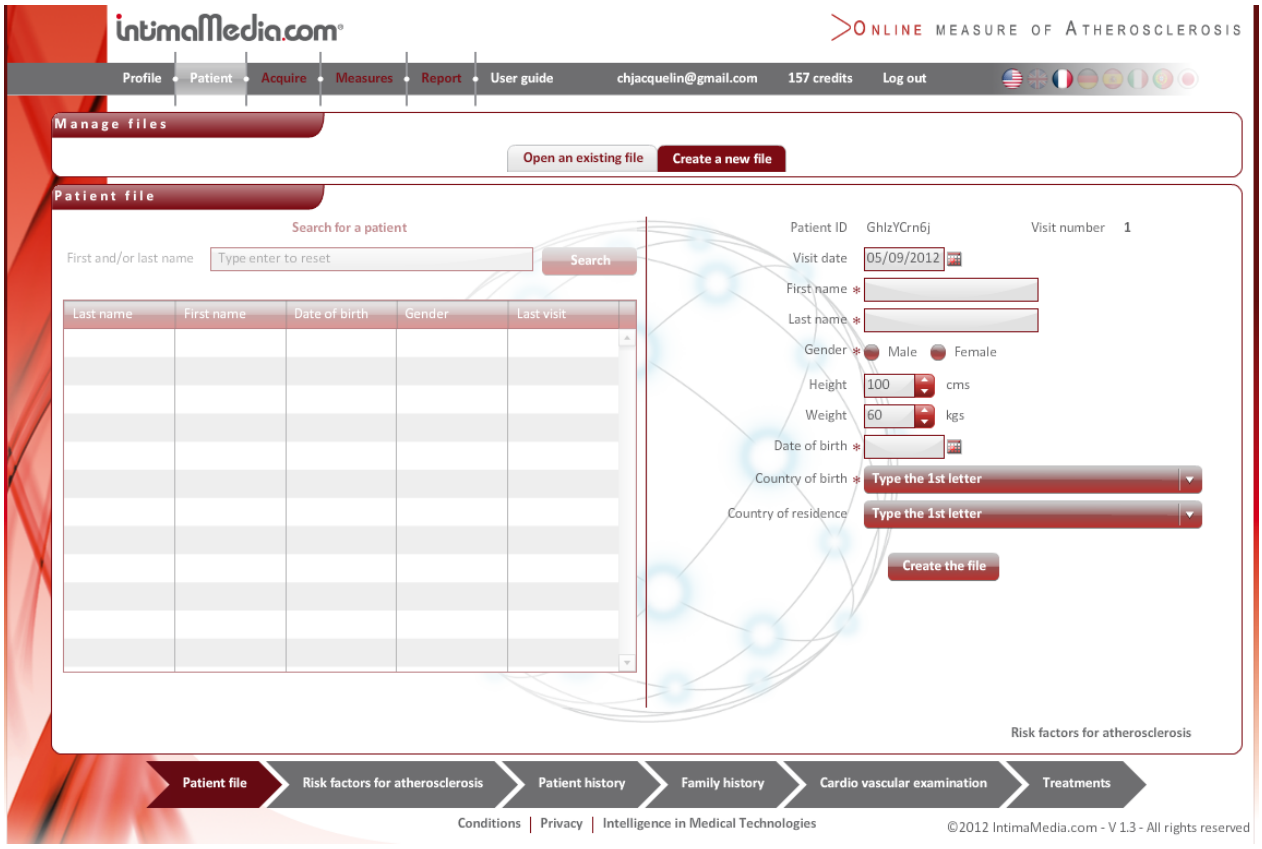
- Patient Identification.
- Atherosclerosis Risk factors.
- Personal Medical History.
- Family history.
- Current Drugs taking.
- Cardiovascular examination.

Below are the corresponding screen captures:



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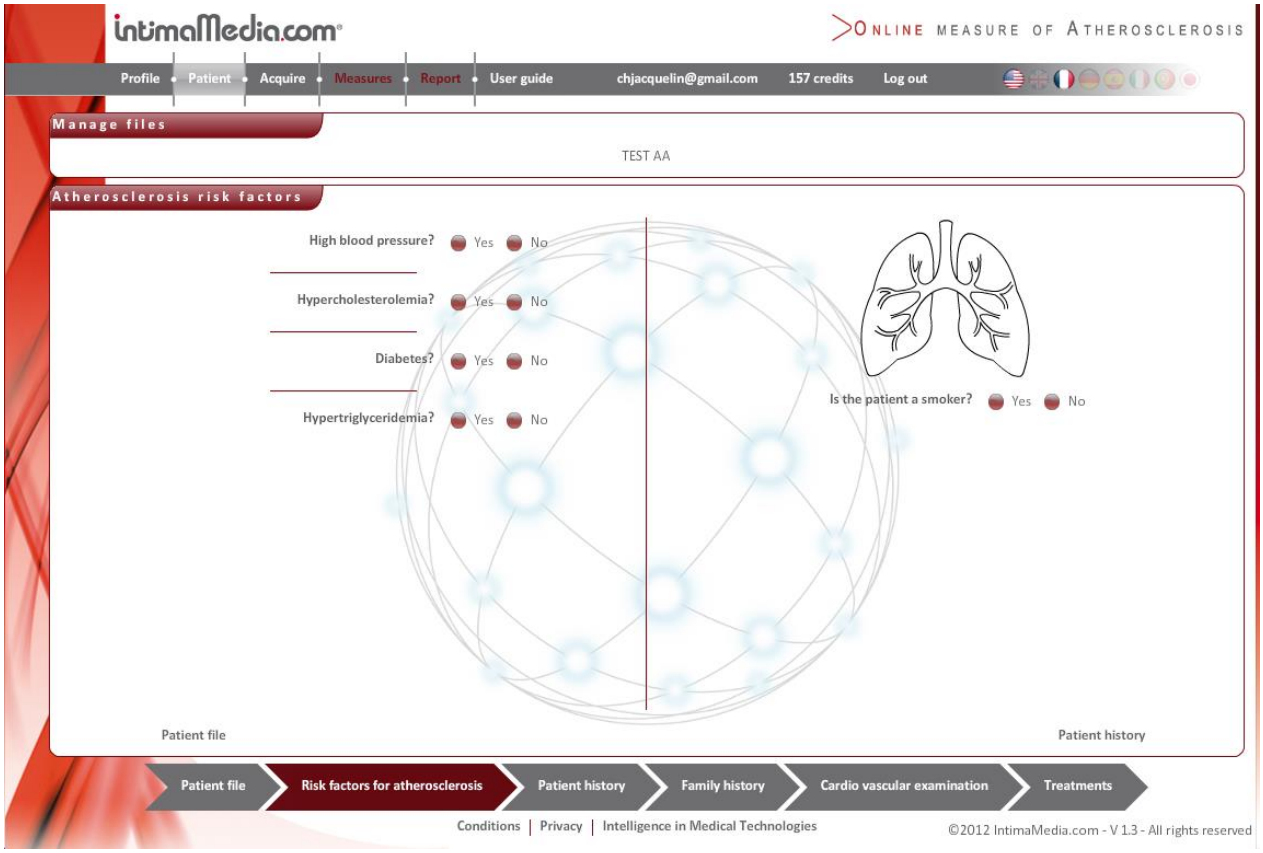

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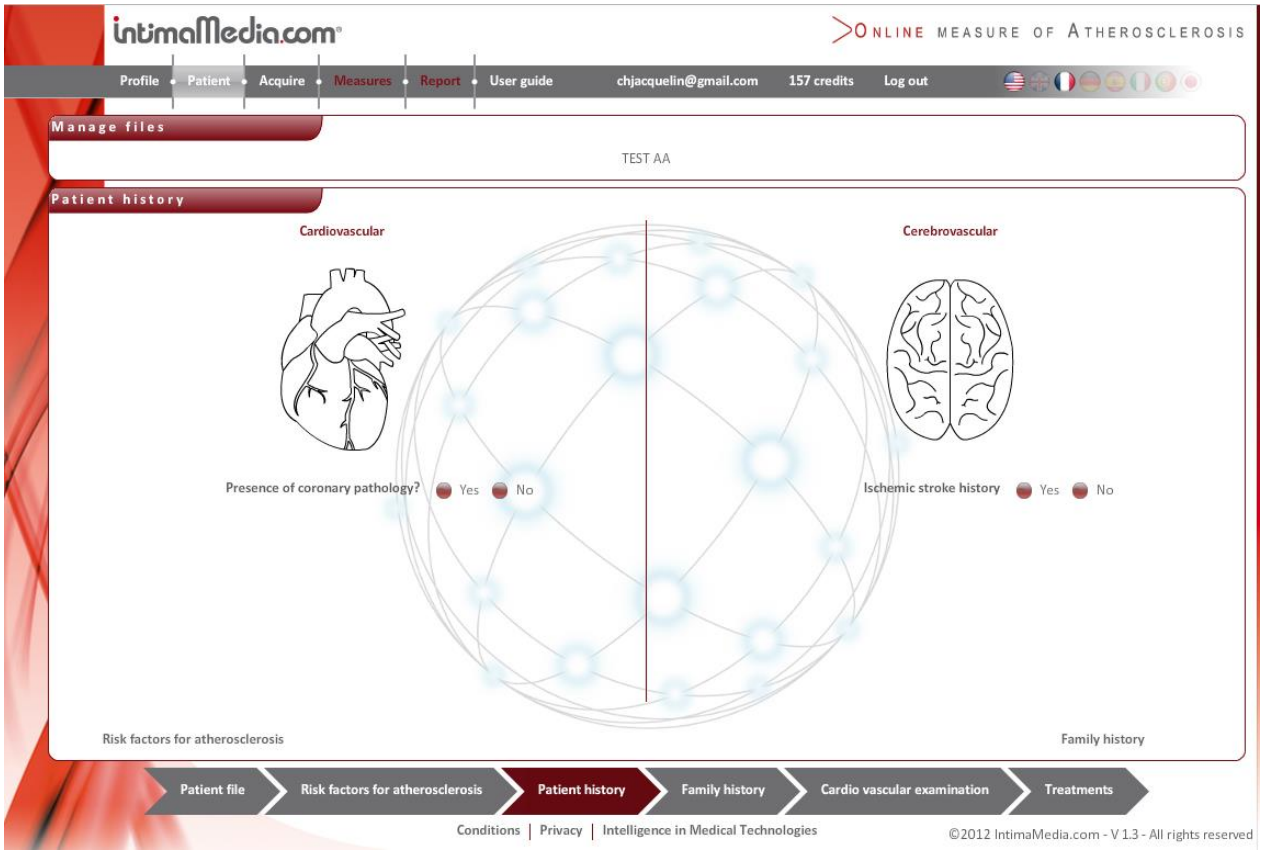

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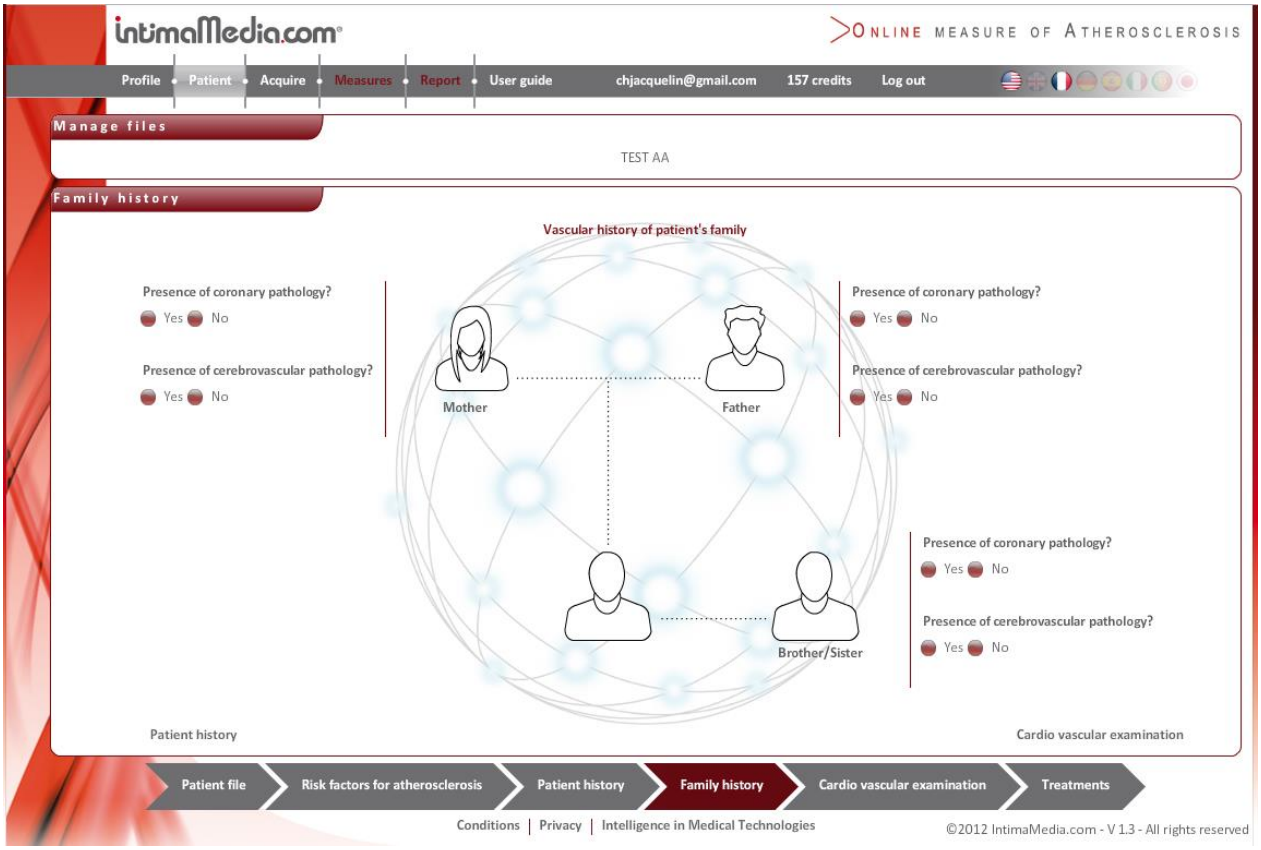

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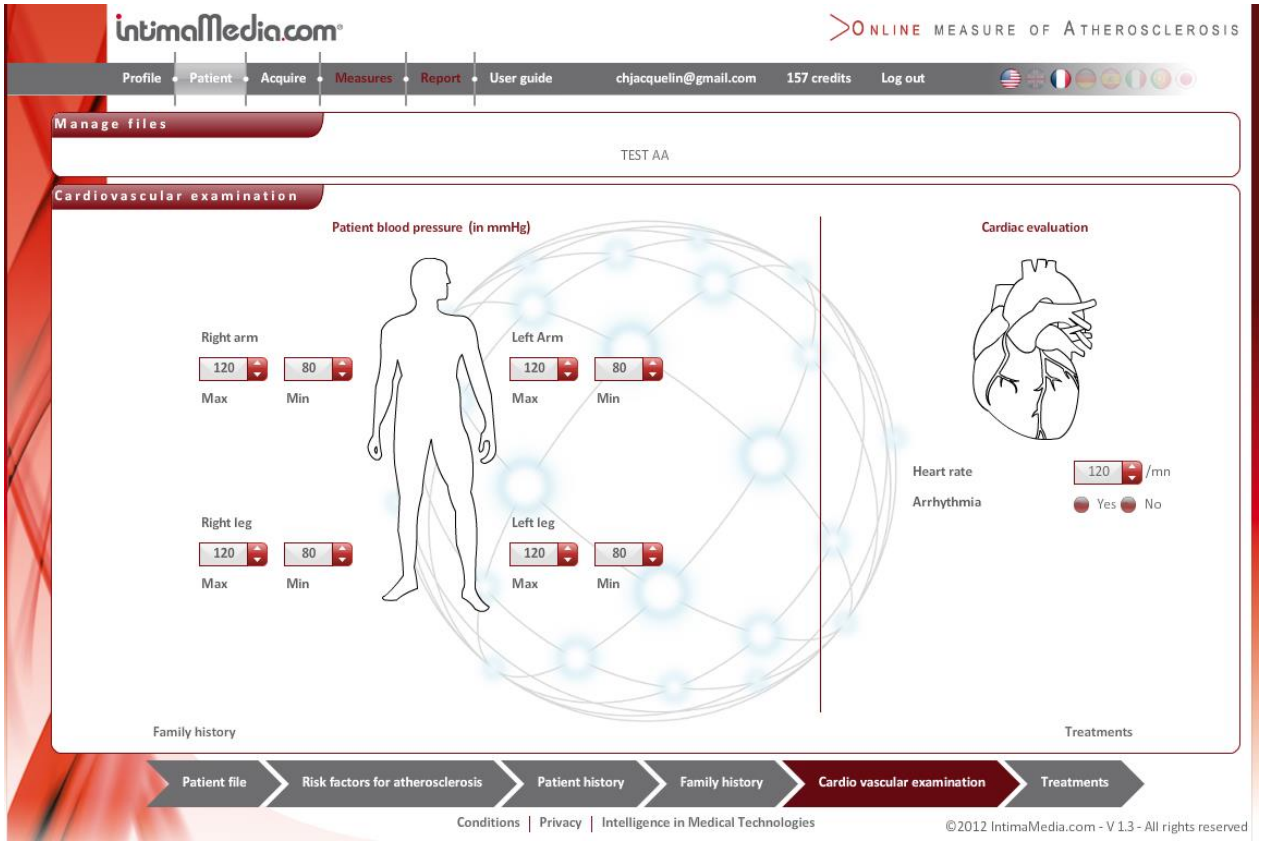

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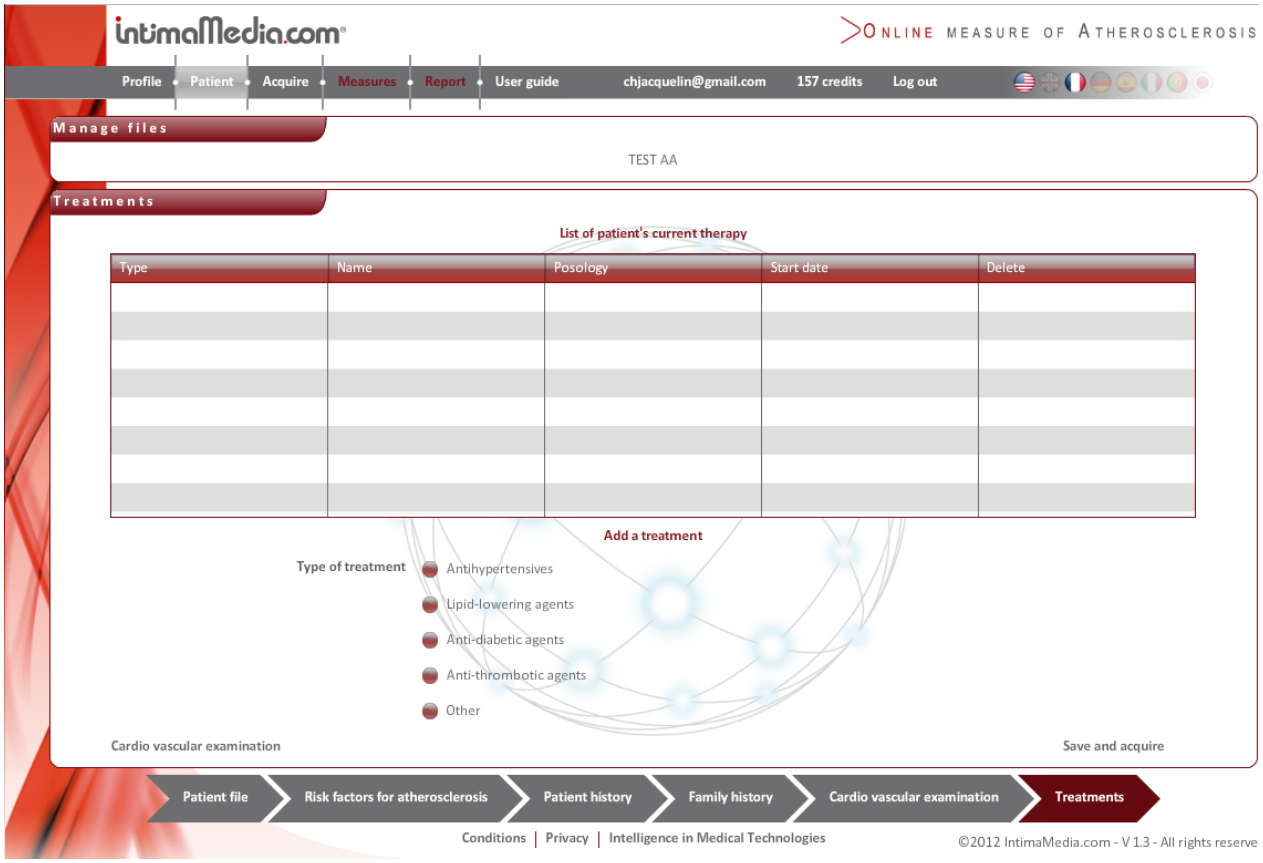

Covered Specifications	5.1, 5.2, 53

Associated Risk	N/A

Risk management:

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3.6 Graphical User Interface: Acquire Tab

Once the user clicks on the button OK in the patient Tab, he (she) can access to this acquisition menu.

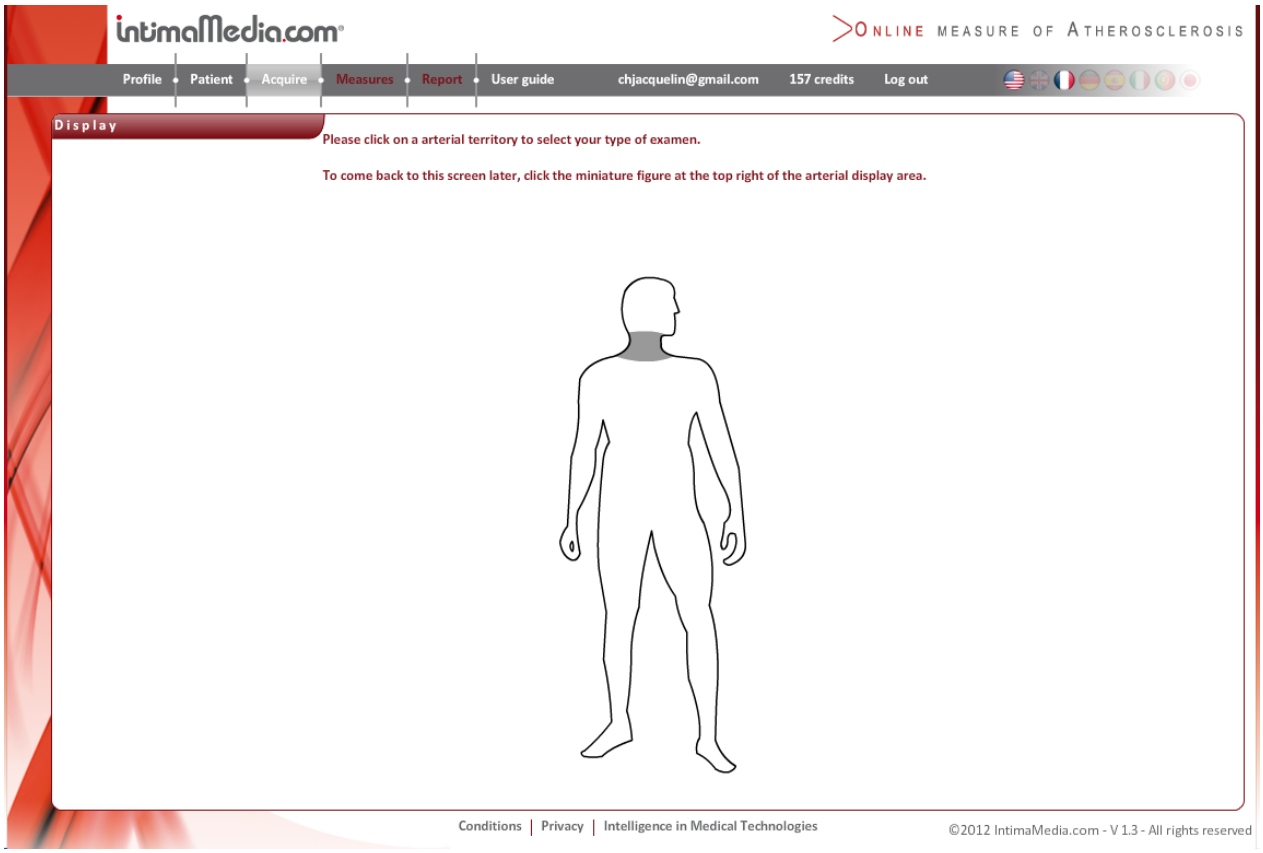
There are two ways to acquire the patient images:

1) – Clicking on the button Browse Images will allow the user to upload image from any drive, of his computer (C.D; E …) to the application.

2) – Clicking on the button Video stream allows the user to capture image coming from an ultrasound device connected to its computer or another video source.

Below is the interface screen shot for image acquisition:

First screen is the selection of the human area.



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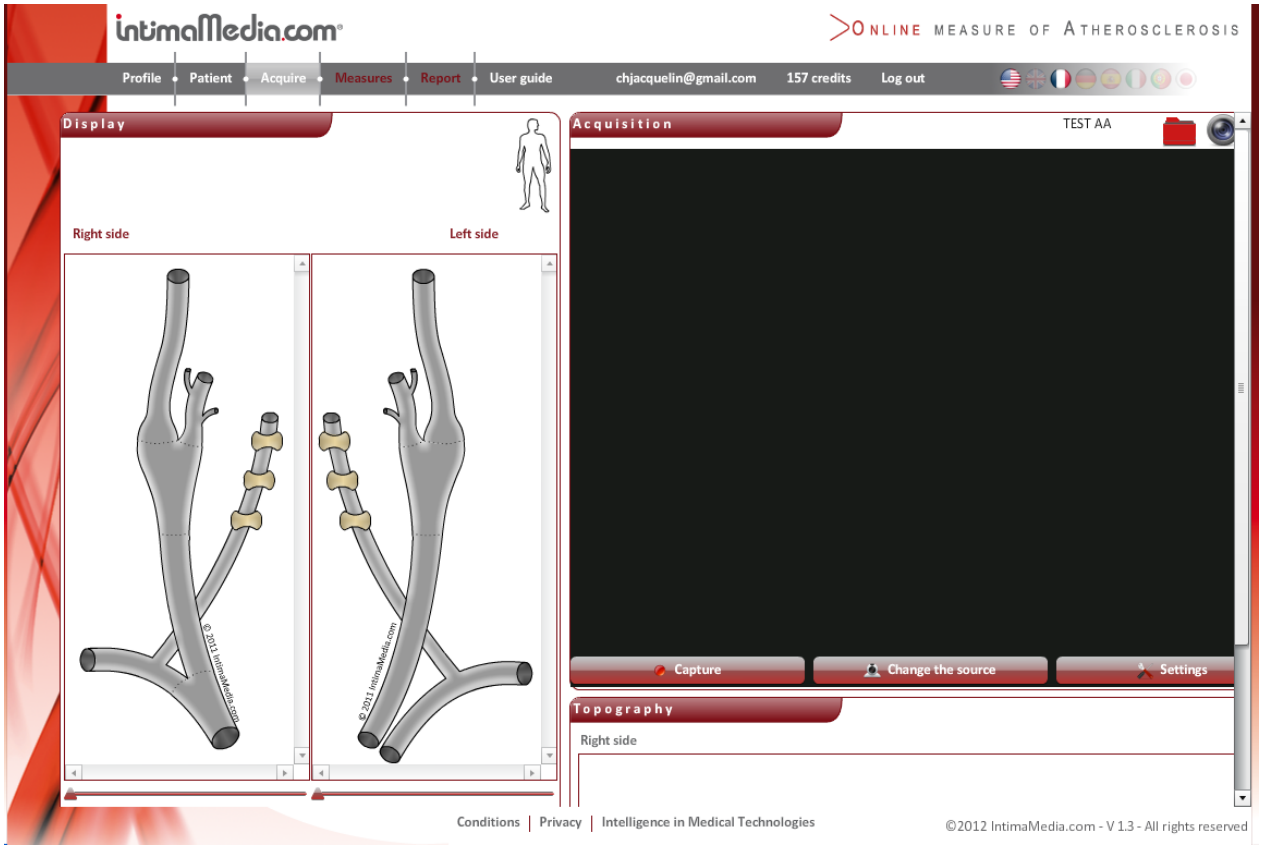

To download an image already on its computer, the user clicks on Browse image, then an open file dialog is opening, and he chooses the location on the file on its computer hard disk or a local network.

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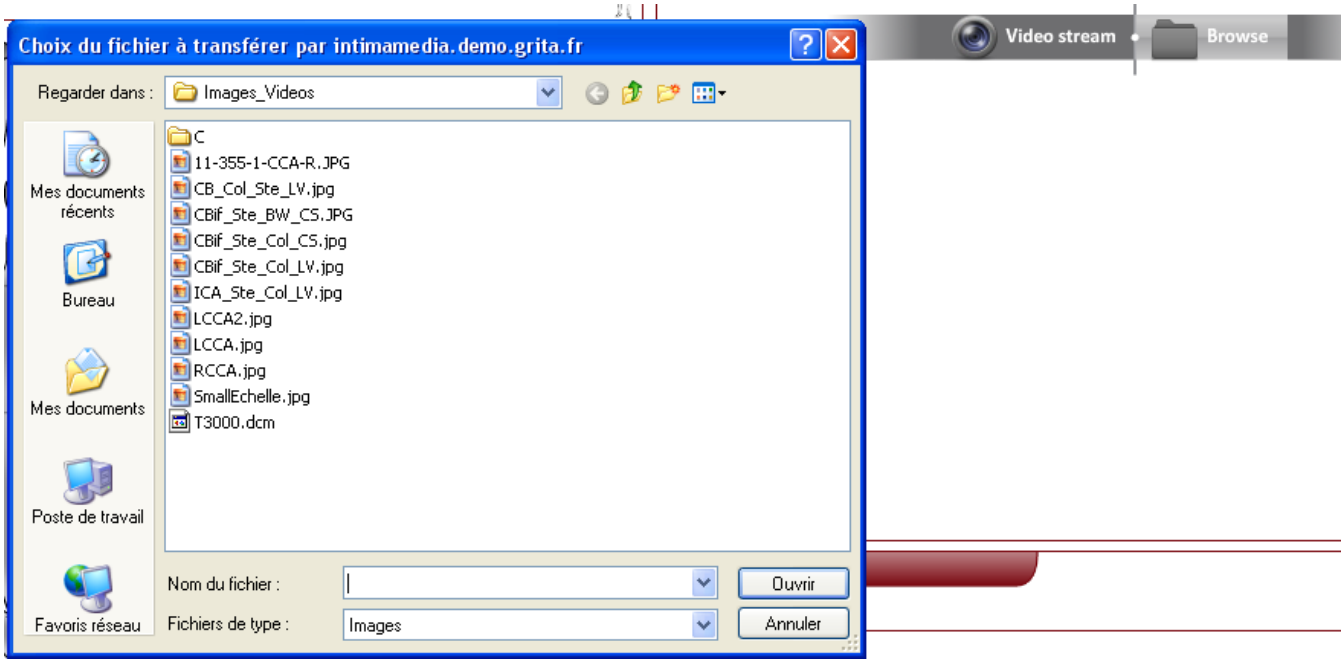
The Open File Dialog is showing below:

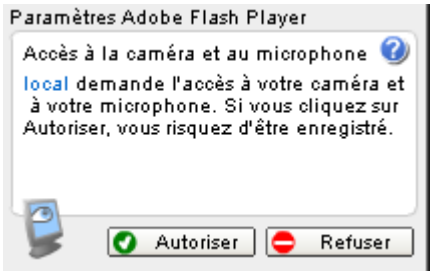


Then, the selected image is downloaded to the Server, and displayed in the window.

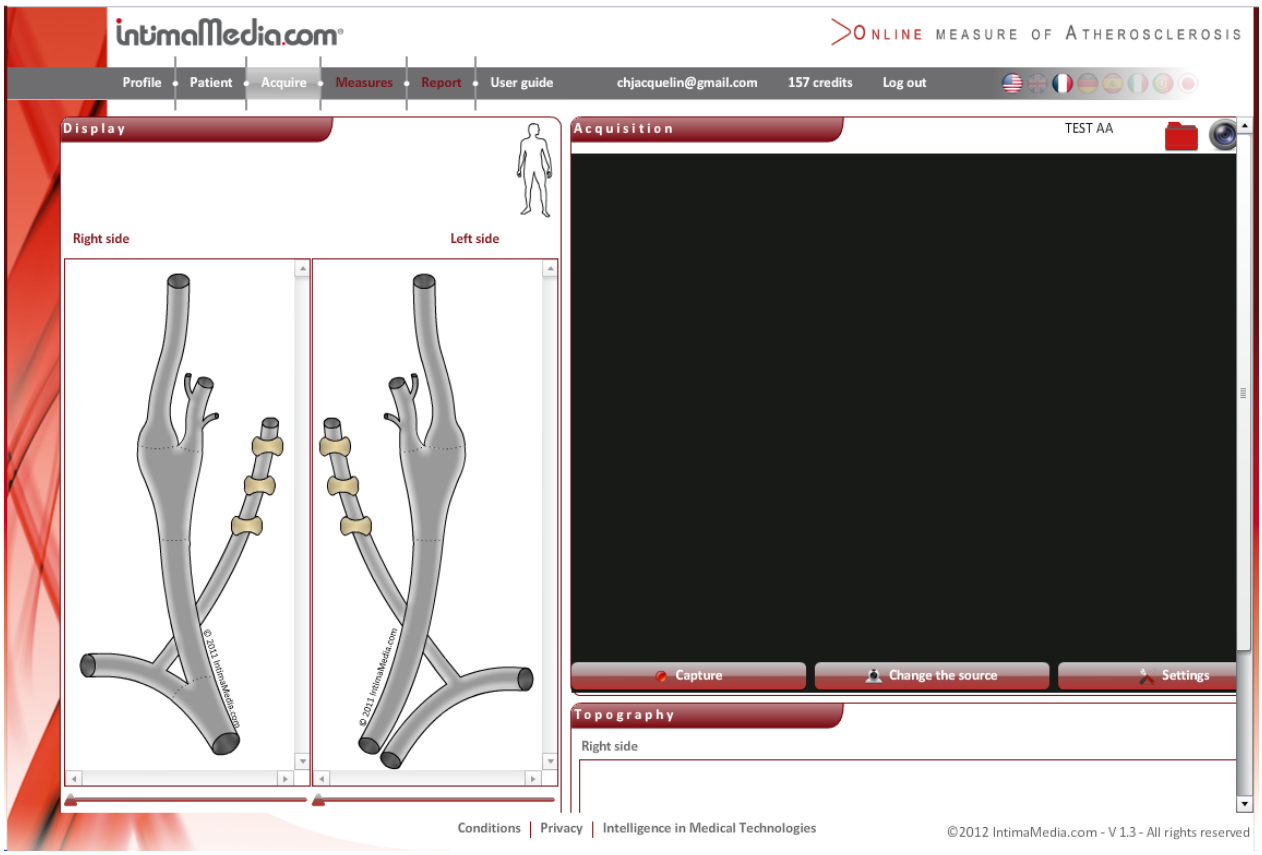
To capture an image coming from an ultrasound device connected to his computer, the user has to connect the ultrasound device to the Analog to Digital converter (Dazzle) or an Osprey Acquisition card. On the

ultrasound machine side the connector will be an RCA BNC or Y/C connector, on the PC side it will be the USB port. The user can also use the Telemed ultrasound system with a driver build on a virtual webcam.

At the first use of the application, Flash Player, for a security reason, is asking for an access agreement:



Then the ultrasound video sound is displayed in live in the bottom window:



The user can freeze the stream to acquire an image, by a click on the capture button. Then the image is displayed in the window.

If there are several possible video acquisition connected to the PC, the user can select one in the list of installed devices (button: Change the source).

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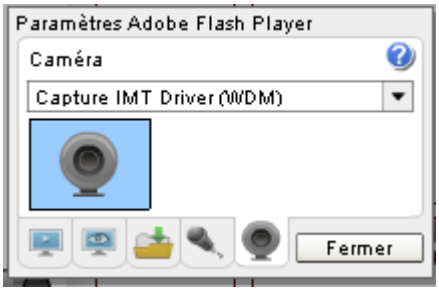
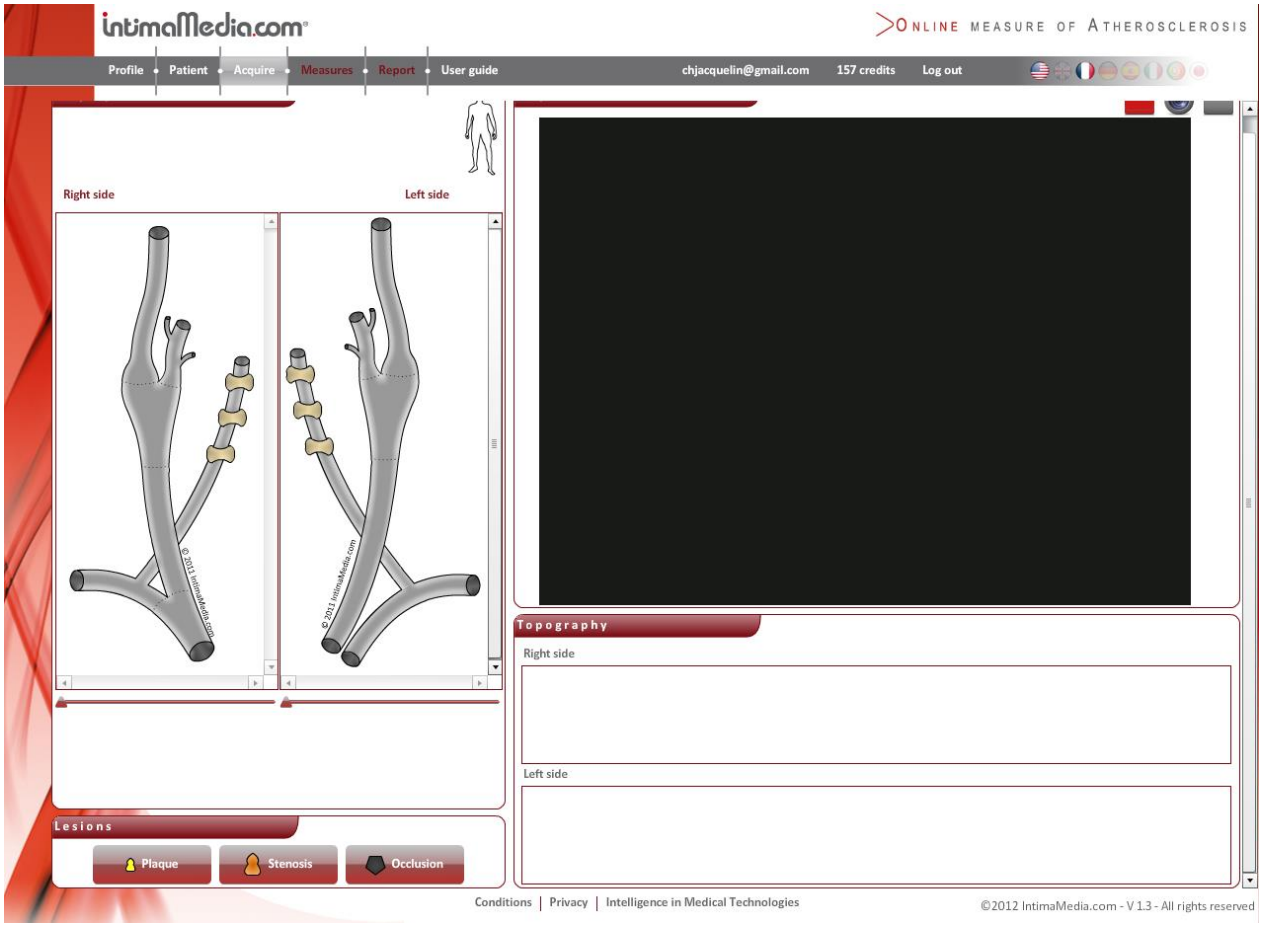


The left part of this page concerns more specifically the positioning of the acquired images and the drawing of graphical events like Plaques, Stenosis or Occlusions.

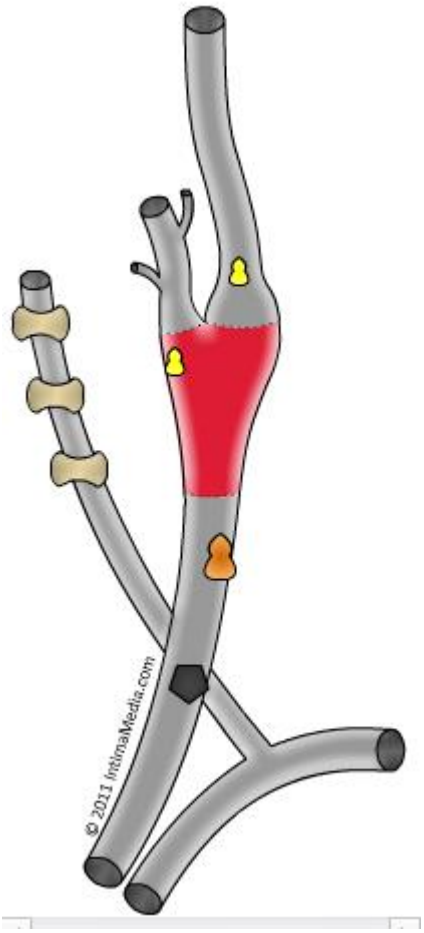


The user acquires images, then he (she) drags and drops images from the right to the left and places each image at the corresponding anatomical site. There are several possible positions, the four upper positions can be longitudinal or cross sectional. the situations can be:

- Internal Carotid Artery.
- Carotid Bifurcation.
- Common Carotid Artery.

If the user wants to change one lesion, he (she) clicks on it to delete.

When a thumbnail is filled, the corresponding arterial segment is filled in red as shown below:



After image acquisition the user can create and manage drawings on both sides representing:

- Plaques
- Stenosis
- Occlusions

If there is a Plaque on the Common Carotid artery segment, the user click on the button Plaque, then he (she) moves the cursor to the position of the plaque on the corresponding graphic segment. Then, after a click on the segment which drops the plaque, a symbol appears on this segment. The same functions exist for Stenosis and Occlusion. For stenosis the user will be asked to give a stenosis degree (between 20 and 99%)

Covered Specifications	6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 6.10, 6.11

Associated Risk.	N/A

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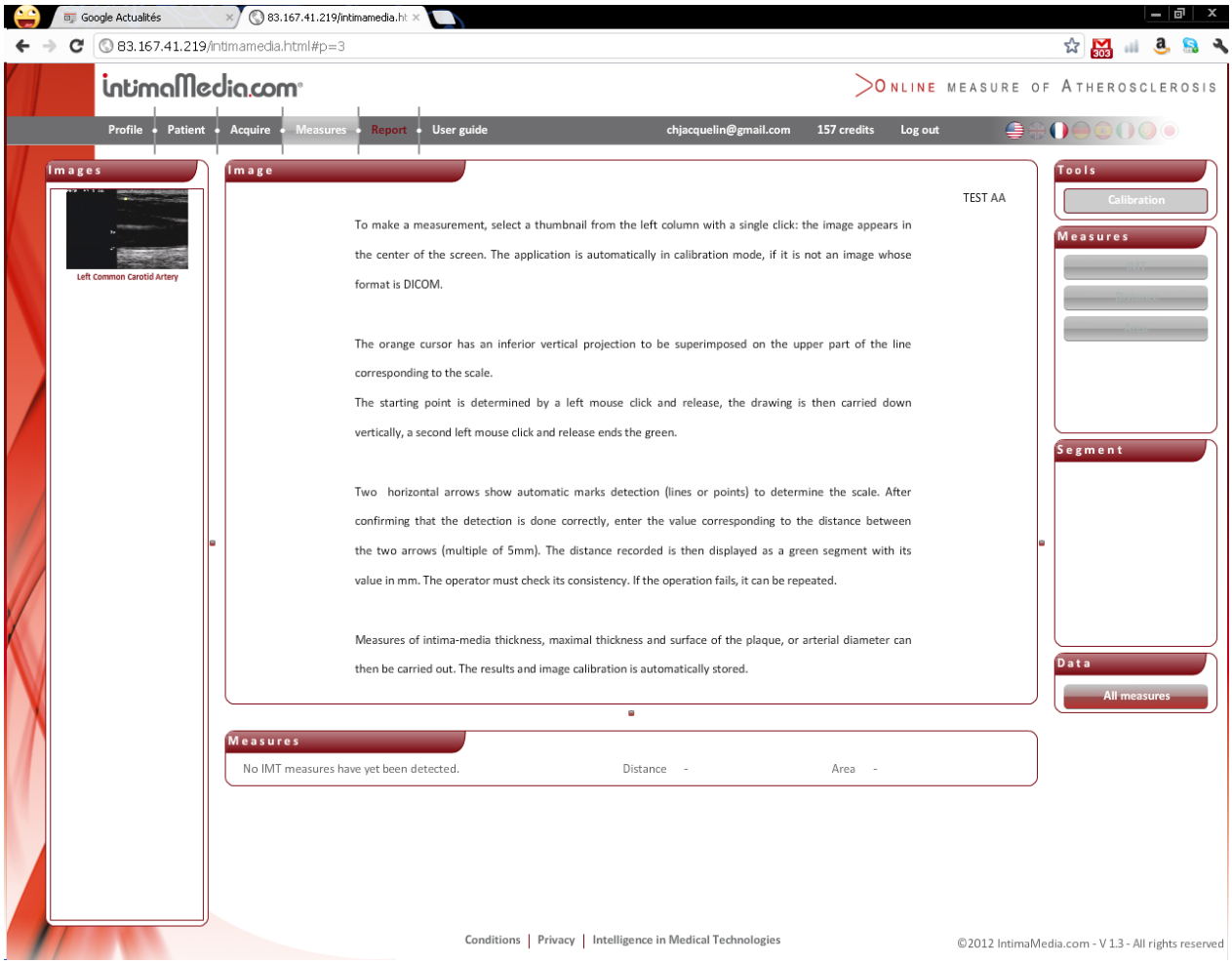
Risk management:

3.7 Graphical User Interface: Measure Tab (MP/CS)

Capture of the measure Tab interface:



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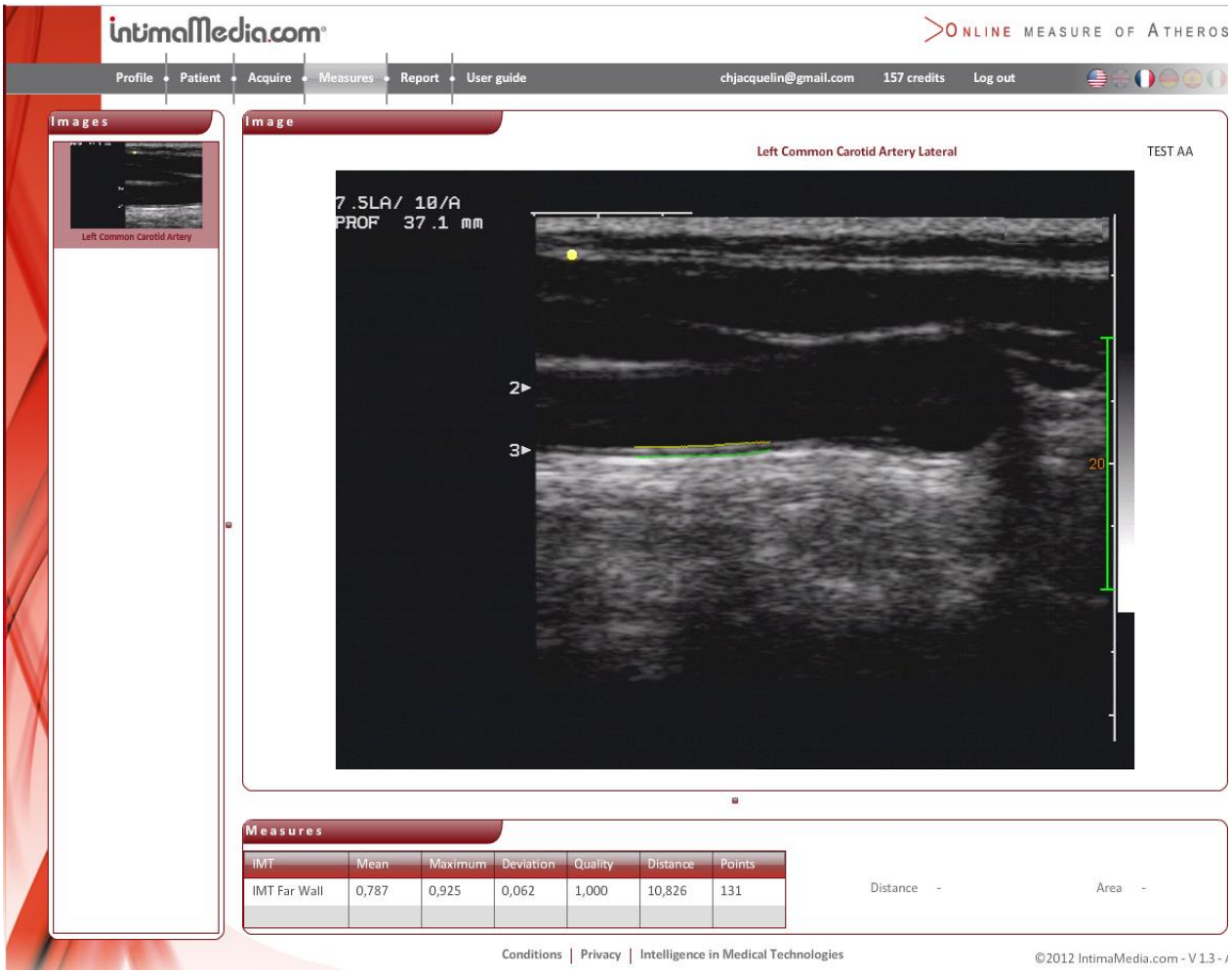

The user can select an image from the left by a click, and then it appears in the main window.

On the top of the image, the command buttons allow respectively for:

- Calibration: to calibrate the application according to the image format
- IMT: to perform an IMT measure on the image.
- Distance: to perform a distance measure on the image.
- Surface: to perform a surface measure on the image.
- All measures: To display array of all the measures for this visit.

On the bottom, there are arrays where resulting measure values are displayed.

When the user clicks on a thumbnail window, the image is displayed, and the application automatically detects scale for this image:

Then the markers are automatically detected by the application and are displayed with red arrows.

The user will have to click on the distance value corresponding to the distance between the red arrows automatically detected:

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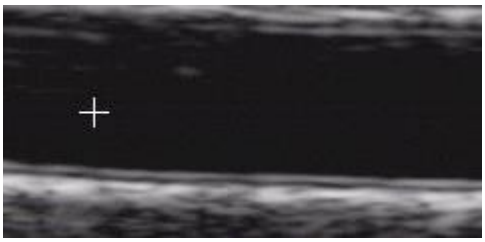
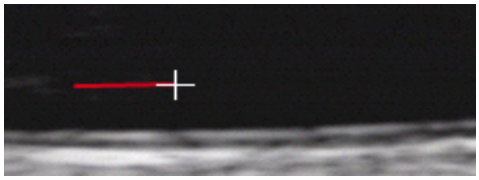
The scale cursor has a line that the user should place on the vertical line scale of the image. This scale cursor is displayed only on the image part. After the first click, the cursor could not move horizontally.

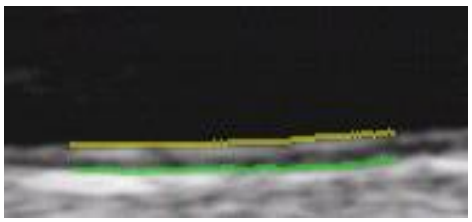
To perform an IMT measure, click on the button “IMT”, then the cursor changes into a white cross, after a first click and release, draw a line parallel to the wall, in a region free of plaque where the IMT is well visible on a distance of 10 mm, 5 to 10 mm below the carotid bifurcation.



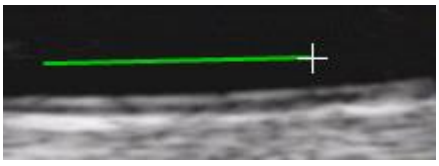
NB: The distance should be under 11 mm.



Then, the IMT measure is computed, and the Intima Media interfaces are displayed in yellow (lumen-intima) and green (media adventitia)



There is a red line which is changing into a green line, when the distance is between 10 and 11 mm.



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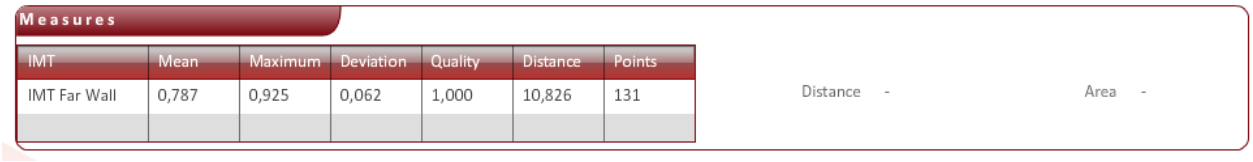
Results of the IMT measurements are displayed on the array at the right beside the image.



On this array:

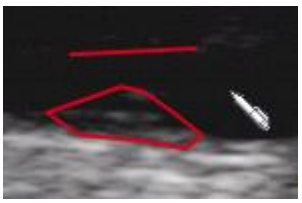
- IMT is the mean IMT value in mm.
- QI is the: Quality Index (from 0 to 1).
- Max is the maximal IMT value (mm).
- Std is the IMT standard deviation
- Pts is the number of points detected on which the measure is computed.

The application helps the user to optimize the IMT measurement, by:

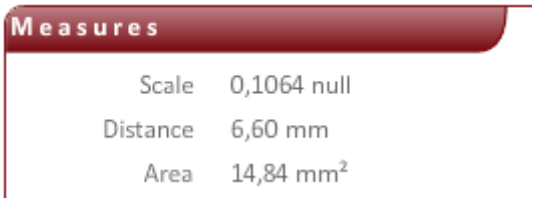
- Indicating with the green line the distance of 10 mm
- Displaying a warning message when the Quality index is under 0.5, or the distance does not reach 10 mm.
-

Displaying in red the QI and distance fields when they are too low. (<0.5)

To perform a distance measure, click on the button “Distance”, then click on 2 points on the image and the distance is displayed in the array on the right.



To perform a surface measure, click on the button “Surface”, then click on points to follow the surface border, then double clicks at the end. The surface (in mm²) is displayed in the array on the right.



To access to the array of measure results, click on the button “Display”. Then, the array below is displayed, providing for each site, measurements and plaque stenosis or occlusion presence.

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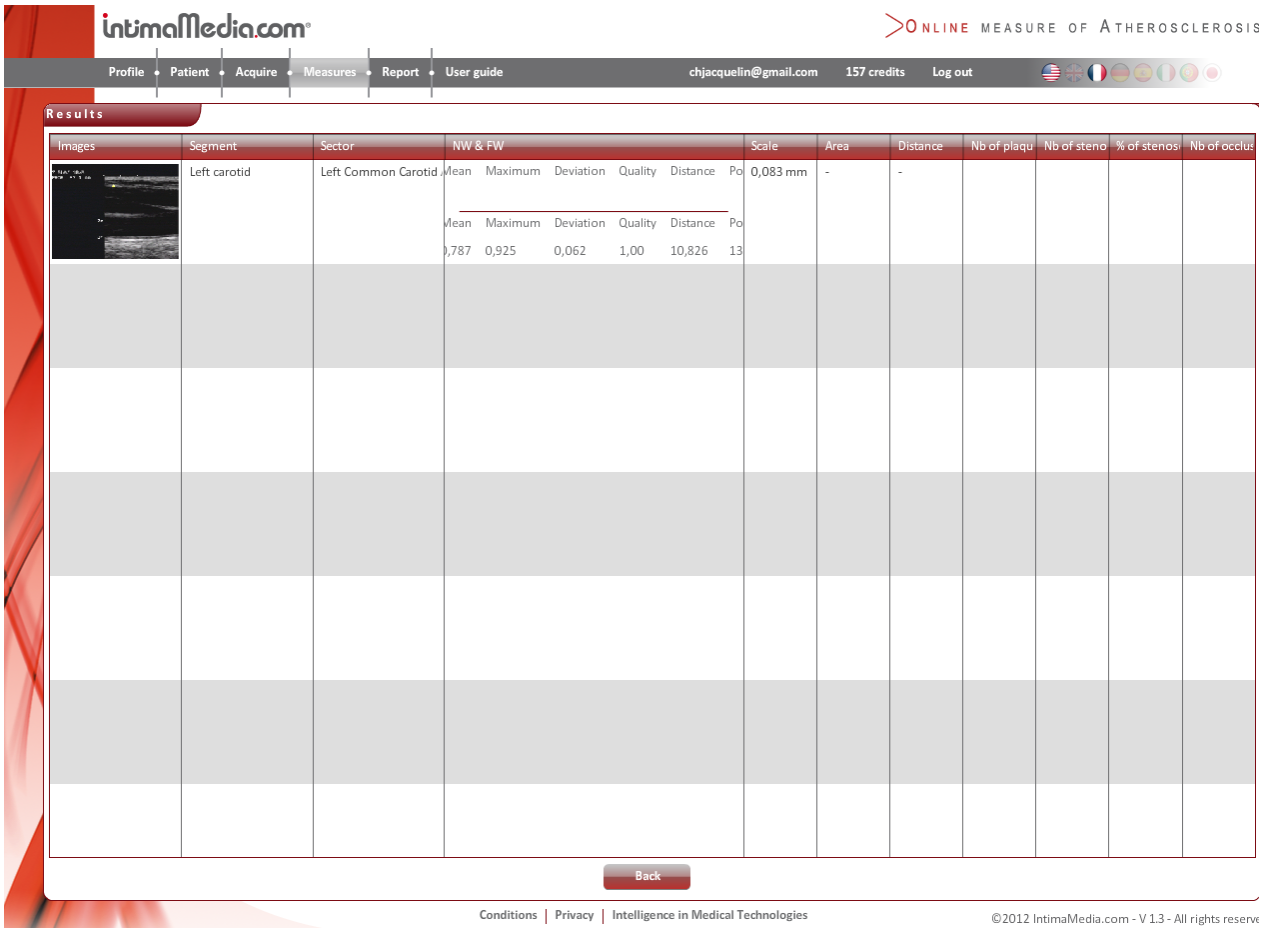

Covered Specifications	7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7

Associated Risk	N/A

Risk management:

3.8 Graphical User Interface: Report Tab (MP)

On this tab, to generate the PDF report file, the user has to click on the button “PDF Adobe”. The user can click on the button at the bottom to download Acrobat Reader to display the report. The user can click on the button “Mail” to send by Email PDF visit report.

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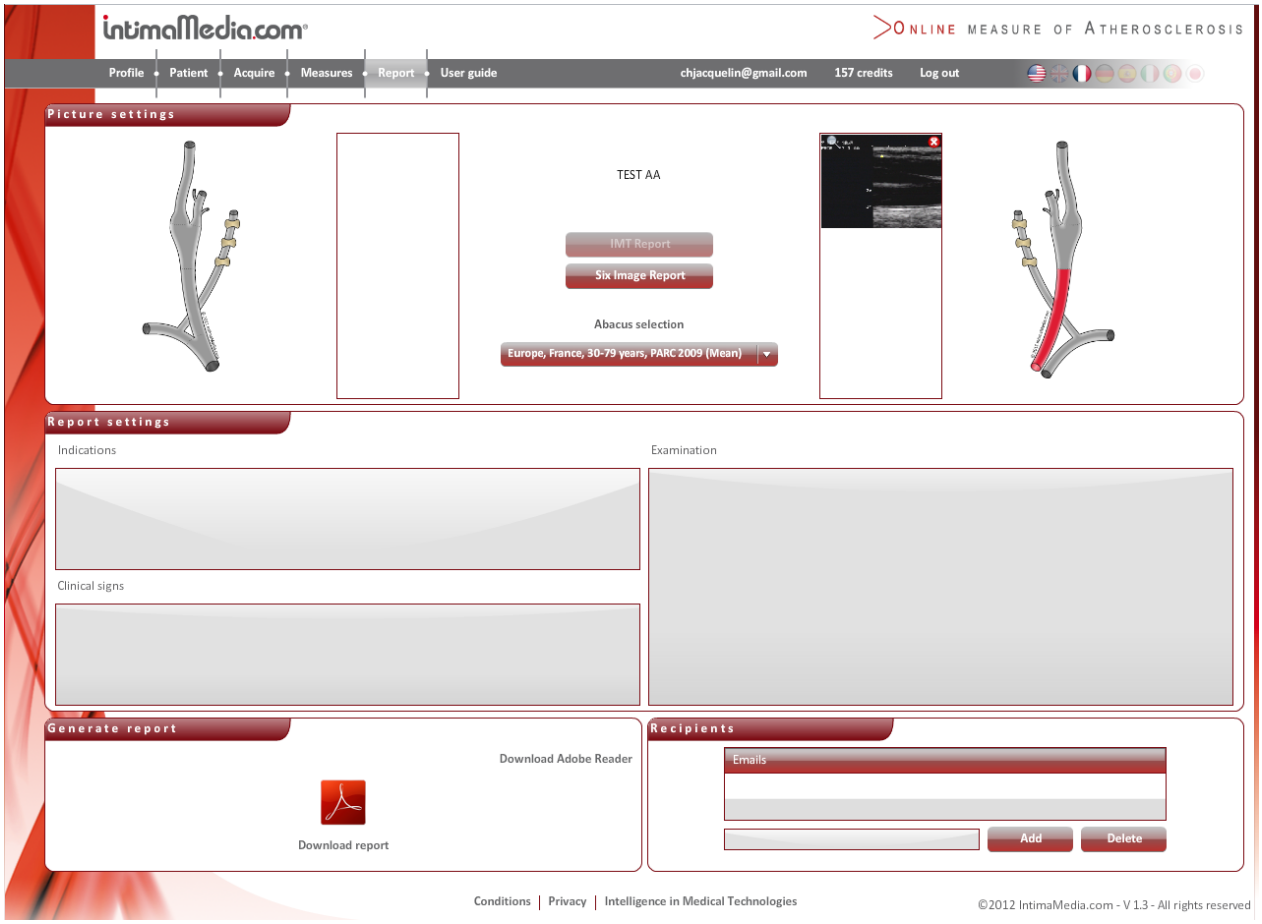

There are 2 types of visit report: A IMT scan report and a multi-images IMT Report.

The multi-images IMT Report is similar to the one generated by the stand alone application M'Ath, and is made of 3 pages:

- Page 1: Images and drawings.
- Page 2: Tables including measure results with ARIC (Usa) or PARC (France) study reference values. Other table of normal values are also possible.
- Page 3: Information on IMT dedicated to the patient.

The report should contain the IMT values, the surface and the stenosis degree for each position.

Report

Report Pages:

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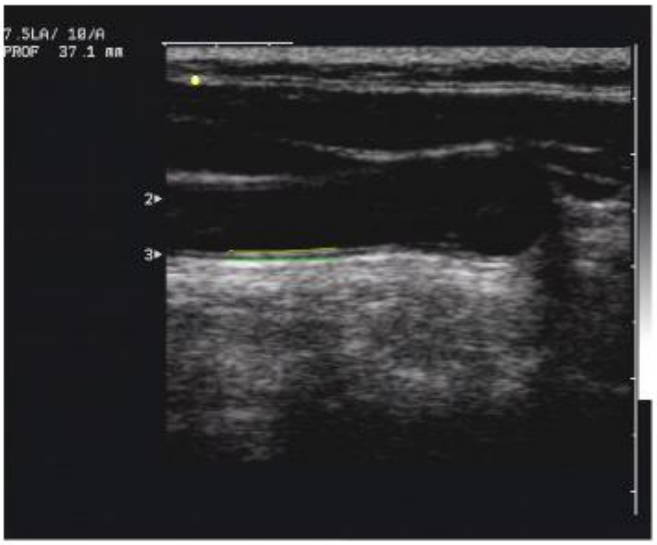
IMT Echography Report

Patient ID :	yUc1QdRzTj	Patient name :	Test VP
Date of birth :	10/04/1960	Visit number :	16
Organization or Office :	IMT	Physician :	VP test

Right

Intima Media Thickness. Mean = 0,522 mm, Max = 0,607 mm

Left

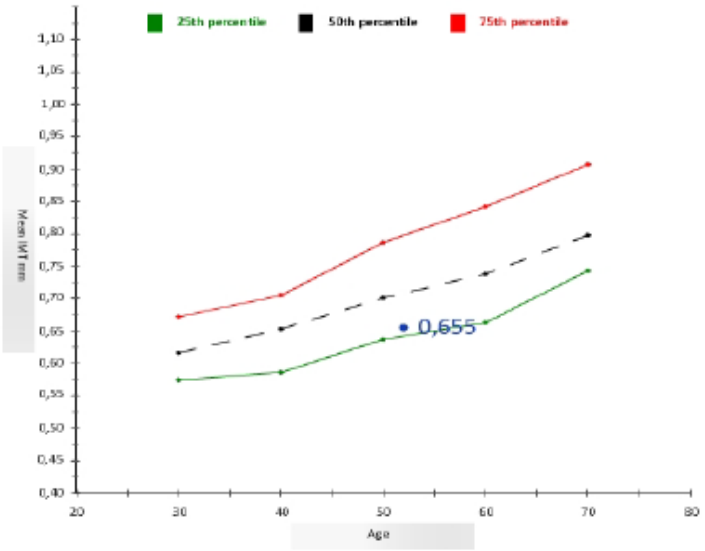


Intima Media Thickness. Mean = 0,788 mm, Max = 0,913 mm

Mean

Age	25th percentile	50th percentile	75th percentile
30	0,574	0,616	0,672
40	0,586	0,653	0,705
50	0,637	0,701	0,787
60	0,663	0,738	0,842
70	0,743	0,798	0,907

Abacus : Europe, France, 30-79 years, PARC 2009 (Mean)



	Right	Left
Distal Mean IMT (mm)	0,522	0,788

Conclusion :

Intima media thickness measurement (IMT)

What is IMT ?

Intima media thickness is made of the 2 first internal layers of the arterial wall: the intima, very thin layer which protects the artery from local deposits of blood components and the media composed of muscle cells which increase their number with high blood pressure. Its representation on ultrasound image a regular double line pattern well seen on the far wall of the common carotid artery.
Plaque is a focal encroachment into the arterial lumen.

Why is it important ?

The non modifiable risk factors that may influence IMT values are age sex and genetics, High blood pressure, lipids, diabetes and smoking are the modifiable factors on which life style modifications and drugs can be recommended.
Increased IMT can predict clinical outcomes as myocardial infarction and stroke. This has been validated by many prospective studies.

How is it measured ?

The conclusions of an international consensus of experts initiated in 2004 and revised in 2006 have precisely defined carotid IMT and plaque.
This consensus recommends measuring IMT at the lower level of the carotid artery called common carotid.
In practice, the ultrasound examination of the carotid artery consists in freezing an image of this artery and automatically measuring it with a software. The results are expressed as the mean value over a 10mm segment of common carotid artery.

When to measure Intima Media Thickness ?

The presence of atherosclerosis risk factors, that is mainly arterial hypertension, dyslipemia, diabetes, smoking or overweight, comes with an increase of IMT in many cases and even more if they are associated.
This measurement shows great information on subjects who have one or more risk factors as it reveals when increased a target organ damage and facilitates the individual cardio-vascular risk evaluation. However, there is no need to watch its evolution outside of epidemiological or interventional studies.

Suggestions for maintaining a healthy vascular system.

- Stop smoking.
- Eat a healthy, low fat diet.
- Talk to your doctor if you are overweight to plan the best weight loss strategy for you.
- Maintain good cholesterol levels.
- Maintain blood pressure in a normal range.
- Exercise regularly - even a moderate walking program can be effective.

Covered specifications	8.1, 8.2, 8.3, 8.4, 8.5

Associated Risk	N/A

Risk management:

3.9 Dicom and JPEG image file formats Graphical

Application can read Dicom or Jpeg images. Video captured images are in the Jpeg format.

Dicom images are read through a Php DICOM library made by another company (www.indebug.com). The Flex application is calling this library to read Dicom files and tags.

This library has a good reference, since it is used by the website www.theVisualMD.com.

Covered specifications	9.1, 9.2

Associated risk	N/A

Risk management:

3.10 Measurements

The Flex application use the same code source as the one used by the software M'Ath (build as a library called LibIMT) to measure the IMT. We have used the application Adobe Alchemy, which convert C source code into a swf file that we use as a library in our application. Alchemy is used for computational library in C that need to be used by Flex application, and that's our case.

The cursor changes into a cross allowing to draw a line in the arterial lumen. A line parallel to the visible structure to measure is defined by the user. The structure is always measured at the right of the vector made of the starting point and the end point of the drawn segment.

From this segment, lines perpendicular to the wall identify density profiles characteristics.

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The density of the line across the structure is measured for each pixel between 0 and 255, corresponding to gray levels. Changes in these densities are represented as a characteristic density profile with □ shape.

The first slope corresponds to the first blood-intima interface, the second slope corresponds to the media-adventitia interface. Distance between the midpoints of these two slopes on the projected line profile is the intima-media thickness. Certain conditions, are however necessary to obtain a reliable profile:

□ □ Threshold variation in density of at least 50

□ □ Getting a point defining the maximum length of the first segment,

□ □ Segment corresponding to the decrease in the density

□ □ Second slope with a maximum greater than the maximum of the first slope.

□ □ Upper limit of the maximum value.

Upon detection of interfaces (P1 and P2), point 1 is represented in yellow and point 2 in green. If the profile is not recognized, the value is ignored. Whichever is the distance between the two variations density. The average of measurements corresponding to the length of the line (green) drawn by the operator is calculated. The percentage values accepted is calculated, it is the quality index (QI) and varies between 0 and 1.

The application measures the Intima-Media thickness (IMT) and provides the following results:

- IMT: IMT mean value in mm.
- QI: Quality index (from 0 to 1).
- Max: IMT max value (mm).
- Std: IMT standard deviation
- Pts: Number of points detected.

As described in 3.8, for the IMT measure, the application helps the user to do a good measurement, by indicating if the IQ is under 0.5, and if the distance is not under 10 or over 11 mm.

And the application provides a tool to perform manual measurements of distances and surfaces.

Spécification(s) couverte(s)	10.1, 10.2, 10.3, 10.4, 10.5

Associated risk	P1, U1. 10.1, 10.2, 10.3

Risk management:

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3.11 Calibration

When a Dicom image is downloaded by the application, calibration is automatically done with the Scaling data inside the Dicom file.

In a first time, the application search for the 'PixelSpacing' (0028, 0030) Dicom tag. If it does not exists, then it searchs for the 'Physical Delta X' (0018, 602C) and 'Physical Delta Y' (0018, 602E) Dicom tags, in the fields of the Dicom file ultrasound region.

If none of the above tags are found, (which can be the case for Dicom images with the type: 'Secondary Capture'), the application proposes to the user to make a manual calibration, with markers on the image.

Covered specifications	11.1, 11.2

Associated risk	P1, U1. 10.1, 10.2, 10.3

Risk management:

The calibration is automatically read in the Dicom file.
If the scaling Dicom tags are missing, the user has to do the calibration.
A distance measure made by the user, after calibration, allows to check for the calibration.

3.12 Images and Data securities

The patient first name, Patient last name are encrypted when they are stored in the Database.

Covered specifications	12.1
Associated risk	P1, U1

Risk management:

To protect the customer data (Images and Database) against Hacking, we have organized the following stages:

- Regular backup of the images and the databases.
- Personnal datas (First name, Last Name, DOB) in the Database are encrypted.

3.13 Internationalization

The application is available in the 6 following languages: English, French, Italian, German, Spanish and Portuguese. Resource strings for each language are inside a file.

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English File:

```
HOME=Home
ENTEREMAIL=Enter your Email Address
…

French file:
HOME=Accueil
```


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INTEREMAIL=Entrez votre adresse Email

Covered specifications	13.1

Associated risk	N/A

Risk management:

3.14 Installation

As required, the installation of the web application on the user computer is minimized. When the user logs into the application the last version is automatically downloaded from the server to its computer.

If Flash Player is not installed on the user's computer, the application asks automatically for Flash Player to be installed.

Covered specifications	14.1, 14.2

Associated risk	N/A

Risk management:

3.15 Visit Modification

A visit can be modified after its creation.

Covered specifications	15.1

Associated risk	N/A

Risk management:

3.16 Application version ID

The application version number is displayed on the application main window to verify that the user use the last version. It is to prevent the user to use a version that is not the last one, when the cache memory is not refreshed.

Covered specifications	16.1

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Associated risk	N/A

Risk management:

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