echosens

KÚPNA ZMLUVA

číslo SZU NL 0108

Uzatvorená podľa § 409 - § 470 Zákona č.513/1991 Zb.(Obchodného zákonníka) v znení neskorších predpisov

Čl. 1.
ZMLUVNÉ STRANY

Kupujúci

Názov organizácie:	Slovenská zdravotnícka univerzita v Bratislave
Sídlo:	Limbová 12, 833 03 Bratislava 37, Slovenská republika
Štatutárny zástupca:	Prof. MUDr. Ján Štencl, CSc., rektor
Zriadená:	Zákonom č. 401/2002 Z. z.
Forma hospodárenia:	Štátna príspevková organizácia
IČO:	00165361
DIČ:	2020341895
IČDPH:	nie je platcom DPH
Názov účtu	BÚ-D/193003 SZU Bratislava –SK0020
Bankové spojenie:	Štátna pokladnica
Číslo účtu:	7000300742/8180

(ďalej len „kupujúci“)

Predávajúci

Obchodné meno:	ECHOSENS S.A.
Sídlo	153 avenue d´Italie, 75013 Paris, France
Štatutárny zástupca::	Richard Guillaume
Bankové spojenie:	Banka Société Générale Paris Bourse Adresa 134 rue Réaumur, 75002 PARIS SWIFT/BIC SOGEFRPP
Číslo účtu IBAN:	FR76 30003 00059 00020123679 51
IČO:	
IČ DPH:	FR634 382 091 57
Zapísaný:	Reg. No.: B 438 209 157

(ďalej len „predávajúci“)

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Čl. 2
PREDMET PLNENIA

2.1. Predmetom plnenia je predaj a kúpa **prístroja FibroScan 502 a k nemu patriacich sond (prístroj na meranie elasticity pečene metódou tranzientnej elastografie)** (ďalej len „predmet plnenia") špecifikovaného v cenovej ponuke (príloha č. 1) k súťaži č. SZU PP 0308-. Súčasťou predmetu plnenia tejto zmluvy bude dodanie zariadenia a inštalačné služby, ako sú doručenie, nastavenie, zaškolenie a príslušná dokumentácia vrátane používateľskej príručky, osvedčení o zaškolení a osvedčení o inštalácií na účely záruky.

Čl. 3.
ČAS PLNENIA

3.1. Predávajúci sa zaväzuje dodať kupujúcemu predmet plnenia do 60 kalendárnych dní od podpisu tejto zmluvy.

Čl. 4.
MIESTO PLNENIA

4.1. Miestom plnenia je Slovenská zdravotnícka univerzita v Bratislave, Limbová 12, 833 03 Bratislava 37.

Čl. 5.
CENA ZA PREDMET PLNENIA

5.1. Kúpna cena za predmet plnenia, je určená v súlade so zákonom č. 18/1996 Z. z. o cenách v znení neskorších predpisov a vyhlášky MF SR č. 87/1996 Z. z. dohodou ako cena maximálna vo výške:

	€
Celková cena bez DPH	**72 190,00**
Celková cena s 19% DPH (len pre informáciu)	85 906,10

5.2. Uvedená cena v € sa rozumie vrátane dopravných nákladov, montáže a uvedenia predmetu plnenia do prevádzky, zaškolenia obsluhujúceho personálu, dodania technickej a servisnej dokumentácie vrátane používateľskej príručky, návodu na údržbu a návodu na obsluhu v anglickom jazyku. Nezahŕňa clo ani DPH.

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Čl. 6.
PLATOBNÉ PODMIENKY

6.1. Cenu za predmet plnenia uhradí kupujúci na základe faktúry – daňového dokladu vystavenej po kompletnej dodávke predmetu plnenia. Neoddeliteľnou súčasťou faktúry budú dokumenty podľa čl. 7.

6.2. Účtovný doklad (faktúra) musí obsahovať

a. označenie povinnej a oprávnenej osoby, adresa, sídlo, IČO, DIČ predávajúceho (na účely DPH)
b. číslo faktúry
c. deň odoslania, deň splatnosti faktúry a deň dodania
d. označenie peňažného ústavu a číslo účtu, na ktorý sa má platiť
e. celková cena bez DPH
f. rozpis fakturovaných čiastok
g. označenie dodávky tovaru, výrobkov
h. pečiatka a podpis oprávnenej osoby
i. body f. a g. budú uvedené v dodacom liste, ktorý bude tvoriť prílohu k prvej faktúre

6.3. Faktúru treba vystaviť v 2 rovnopisoch.

6.4. Splatnosť faktúry je 15 pracovných dní odo dňa vystavenia a pred montážou a zaškolením.

6.5. V prípade, že faktúra nebude obsahovať náležitosti uvedené v tejto zmluve, kupujúci je oprávnený vrátiť ju predávajúcemu na doplnenie. V takom prípade sa preruší plynutie lehoty splatnosti a nová lehota splatnosti začne plynúť doručením opravenej faktúry kupujúcemu.

Čl. 7.
SPLNENIE PREDMETU PLNENIA

7.1. Splnením predmetu plnenia podľa čl. 2. tejto zmluvy sa rozumie splnenie bodov dodanie, inštalácia a zaškolenie obsluhy o čom bude urobený preberací protokol.

Čl. 8.
ZÁRUČNÁ DOBA

8.1. Predávajúci ručí za vlastnosti predmetu plnenia tejto zmluvy, ktoré uviedol v ponuke pre predmetnú zákazku (príloha č. 2), po dobu 2 rokov odo dňa splnenia predmetu plnenia.

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Čl. 9.
ZÁRUČNÝ A POZÁRUČNÝ SERVIS

9.1. Zmluvné strany sa dohodli pre prípad vady zo záruky predmetu plnenia, že počas záručnej doby má kupujúci právo požadovať a predávajúci povinnosť poskytnúť bezplatné odstránenie záručnej vady a prípadne si uplatniť ďalšie práva v zmysle § 436 Zákona č. 513/1991 Zb. Obchodného zákonníka v znení neskorších predpisov. Výnimkou je vada, ktorá vznikla poškodením predmetu plnenia, hrubou nedbanlivosťou kupujúceho pri jeho manipulácii, alebo jeho konaním v rozpore s inštrukciami ohľadne používania predmetu plnenia.

9.2. Predávajúci sa zaväzuje začať s odstraňovaním prípadnej záručnej vady predmetu plnenia v zmysle bodu 8.1 bez zbytočného a neodôvodneného odkladu a záručné vady odstrániť v čo najkratšom čase. Termín odstránenia vady sa dohodne písomnou formou.

9.3. Ak sa ukáže, že vada predmetu plnenia je neopraviteľná, zaväzuje sa predávajúci dodať do 90 kalendárnych dní náhradný predmet plnenia, bez manuálu v slovenskom a anglickom jazyku a zaškolenia obsluhy. Neopraviteľnou záručnou vadou sa rozumie vada, ktorú predávajúci deklaruje ako neopraviteľnú svojim písomným vyjadrením do 30 dní od nahlásenia záručnej vady kupujúcim písomnou formou.

9.4. Kupujúci sa zaväzuje, že prípadnú reklamáciu vady predmetu plnenia uplatní bezodkladne po jej zistení písomnou formou (listom, faxom, emailom) predávajúcemu.

Čl. 10.
ZMLUVNÉ POKUTY

10.1. V prípade nedodania predmetu plnenia predávajúcim v dohodnutom termíne, môže si kupujúci nárokovať úroky z omeškania i zmluvnú pokutu z omeškania vo výške 0,01% z ceny celkom podľa bodu 5.1 za každý aj začatý deň omeškania.

10.2. Ak predávajúci nezačne s odstraňovaním záručnej vady v čase podľa bodu 9.2, uhradí predávajúci kupujúcemu zmluvnú pokutu vo výške 0,01% z ceny celkom podľa bodu 5.1 za každý aj začatý deň omeškania.

10.3. V prípade, ak kupujúci nebude uhrádzať predávajúcemu cenu predmetu tejto zmluvy tak, ako je uvedené v čl. 6. tejto zmluvy, môže si predávajúci nárokovať úroky z omeškania z dlžnej čiastky vo výške 0,01% za každý deň omeškania.

10.4. Nárok na zmluvnú pokutu a úrok z omeškania nevzniká vtedy, ak sa preukáže že:

- omeškanie je spôsobené účinkom vyššej moci, alebo
- omeškanie je spôsobené druhou zmluvnou stranou.

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10.5. V prípade, že predmet zmluvy nemôže byť predávajúcim expedovaný v dohodnutom termíne z dôvodov zavinených kupujúcim, je predávajúci oprávnený vyžadovať zdokladovanú náhradu škody počínajúc piatym týždňom oneskorenia.

Čl. 11.
OSTATNÉ USTANOVENIA

11.1. Predávajúci bude pri plnení predmetu plnenia postupovať s odbornou starostlivosťou. Zaväzuje sa dodržiavať všeobecne záväzné právne predpisy, technické normy a podmienky tejto zmluvy.

11.2. Predmet plnenia zostáva majetkom predávajúceho do splatenia ceny.

11.3. Nebezpečenstvo škody na predmete plnenia prechádza na kupujúceho po splnení Čl. 7.

Čl. 12.
ZÁVEREČNÉ USTANOVENIA

12.1. Zmluva vzniká a je uzavretá okamihom, kedy je posledný súhlas s obsahom návrhu zmluvy doručený druhej zmluvnej strane. Zmluva vzniká prejavením súhlasu s celým jej obsahom. Súhlas musí byť písomný a podpísaný oprávneným zástupcom zmluvnej strany, ktorá ho prejavila.

12.2. Meniť alebo doplňovať text tejto zmluvy je možné výlučne len formou písomných dodatkov, ktoré budú platné, ak budú riadne potvrdené a podpísané oprávnenými zástupcami oboch zmluvných strán.

12.3. K návrhom dodatkov k tejto zmluve sa zmluvné strany zaväzujú vyjadriť písomne, v lehote 15 dní od doručenia návrhu dodatku druhej strane.

12.4. Táto zmluva sa riadi právnym poriadkom Francúzska.

12.5. Táto zmluva je vypracovaná v štyroch vyhotoveniach, z ktorých dva si ponechá predávajúci a dva kupujúci.

za predávajúceho
v Paris dňa .....

Jean-Marc David
Manažer globálneho predaja a distribúcie

za kupujúceho
v Paris dňa .....14.05.2009.....

Prof. MUDr. Ján Štencl, CSc.
rektor

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Agreed sales conditions

number SZU NL 0108

Concluded in accordance with Sections 409–470 of Act No. 513/1991 Coll.(Commercial Code) as amended

Art. 1.
PARTIES

Buyer

Name of the organization:	Slovenská zdravotnícka univerzita v Bratislave
Seat:	Limbová 12, 833 03 Bratislava 37, Slovak Republic
Statutory representative:	Prof. MUDr. Ján Štencl, CSc., Chancellor
Established:	by Act No. 401/2002 Coll.
Legal form:	Public Funded Organization
Identification No.:	00165361
Tax identification No.:	2020341895
VAT ID:	not VAT registered
Account name	BÚ-D/193003 SZU Bratislava – SK0020
Bank:	State Treasury
Account number:	7000300742/8180

(the "Buyer")

Seller

Business name:	ECHOSENS S.A.
Seat	153 avenue d´Italie, 75013 Paris, France
Statutory representative:	Mr. Richard Guillaume
Bank:	Société Générale Paris Bourse Bank Address 134 rue Réaumur, 75002 PARIS SWIFT/BIC SOGEFRPP
IBAN number:	FR76 30003 00059 00020123679 51
Identification No.:	
VAT ID:	FR634 382 091 57
Registration number:	Reg. No.: B 438 209 157

(the "Seller")

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Art. 2
OBJECT OF THE AGREEMENT

2.1. This Agreement has for object the sale and purchase of the **FibroScan 502 device and associated features (device for measuring liver elasticity by transient elastography method)** (the "Object of the Agreement") specified in the bid (Annex No. 1) relating to tender No. SZU PP 0308-. The Object of the Agreement shall also include supplying equipment and installation services such as delivery, set-up, training and relevant associated documents including user's manual, training certificates and installation certificates for warranty purposes.

Art. 3.
COMPLETION PERIOD

3.1. The Seller undertakes to deliver the Object of the Agreement to the Buyer within 60 calendar days following the signing hereof.

Art. 4.
COMPLETION PLACE

4.1. Delivery shall be made to: Slovenská zdravotnícka univerzita v Bratislave, Limbová 12, 833 03 Bratislava 37.

Art. 5.
PRICE FOR THE OBJECT OF THE AGREEMENT

5.1. The purchase price for the Object of the Agreement is determined by agreement in accordance with Act No. 18/1996 Coll. on Prices as amended by later regulations and Decree of the Ministry of Finance of the Slovak Republic No. 87/1996 Coll. as the maximum price amounting to:

	€
Total price excluding VAT	**72 190,00**
Total price with VAT 19% (for information only)	85 906,10

5.2. The price specified in € shall include transportation costs, installation and activation of the Object of the Agreement, operator training, delivery of the technical and maintenance documents including manuals, service and operating instructions in English. It doesn't include either duty, or VAT.

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-Art. 6.
PAYMENT TERMS

6.1. The price for the Object of the Agreement shall be paid by the Buyer against an invoice issued following the complete delivery of the Object of the Agreement. In accordance with Art. 7, these documents shall be an integral part of the invoice.

6.2. The accounting document (invoice) shall include :

a. designation of a responsible person and his legal representative, address, seat, identification No. and tax identification No. of the Seller (for VAT purposes)
b. invoice number
c. date of issue, due date of the invoice and delivery date
d. designation of the financial institution and account number to which the price shall be credited
e. total price excluding VAT.
f. itemization of the invoiced amounts
g. list of goods and products supplied
h. stamp and signature of the legal representative.
i. items f. and g. shall be specified in the delivery note which shall be attached to the first invoice

6.3. The invoice shall be issued in 2 copies.

6.4. The invoice payment date shall be 15 business days following its issuance, and before installation and training on the material.

6.5. If the invoice does not include the necessary data specified herein, the Buyer shall be entitled to return it to the Seller for completion. In such event, the expiry period shall be interrupted and a new one shall begin on the day of the invoice's delivery to the Buyer.

Art. 7.
COMPLETION OF THE OBJECT OF THE AGREEMENT

7.1. **Completion of the** Object of the Agreement under Art. 2 hereof shall mean satisfactory delivery, installation and operator training, according to a prepared acceptance protocol.

Art. 8.
WARRANTY PERIOD

8.1. The Seller's warranty shall apply to the quality of the Object of the Agreement which it specified in the bid for the order in question (Annex No. 2) for a period of 2 years following the delivery date of the Object of the Agreement.

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Art. 9.
REPAIR AND MAINTENANCE WITHIN AND OUTSIDE WARRANTY

9.1. The Parties agree that in the event that the Object of the Agreement is defective during the warranty period, the Buyer shall be entitled to require from the Seller, and the Seller shall be obliged to provide to the Buyer, repairment of the defect free of charge, and, as the case may be, exercise other rights according to Section 436 of Act No. 513/1991 Coll., the Commercial Code, as amended. The defect caused by damage to the Object of the Agreement, Buyer's gross negligence during handling, or actions in conflict with the instructions regarding the normal use thereof, shall be an exception.

9.2. The Seller undertakes to begin to repair any defect within the warranty period in accordance with Section 8.1 in the best possible and reasonable delays, and repair any defects within the warranty period as soon as possible. The deadline for the repair of such defects shall be agreed in writing.

9.3. In the event that it is proven that the defect in the Object of the Agreement can not be repaired, the Seller undertakes to deliver a replacement Object of the Agreement within 90 calendar days, but, without the manual and operator training. A defect which cannot be repaired within the warranty period shall mean a defect which the Seller declares as such in writing within 30 days following the notice on the defect within the written warranty.

9.4. The Buyer undertakes to submit any complaint regarding any defect of the Object of the Agreement to the Seller without undue delay following its detection and in writing (by mail, fax, e-mail).

Art. 10.
CONTRACTUAL PENALTIES

10.1. In the event that the Seller does not deliver the Object of the Agreement within the stipulated period, the Buyer shall be entitled to the default interest amounting to 0.01% of the total price under Section 5.1 for each day of delay or part thereof.

10.2. In the event that the Seller does not begin to repair a defect within the warranty period in accordance with Section 9.2, the Seller shall pay the Buyer a contractual penalty in the amount of 0.01% of the total price under Section 5.1 for each day of delay or part thereof.

10.3. In the event that the Buyer does not pay the Seller the price for the Object hereof as defined in Art. 6 hereof, the Seller shall be entitled to the default interest in the amount of 0.01% of the sum due for each day of delay.

10.4. The right to the contractual penalty and default interest shall not apply if it is proven that:

- the delay was caused by force majeure, or
- the delay was caused by the other Party.

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10.5. In the event that the Object hereof can not be dispatched by the Seller within the agreed period for circumstances caused by the Buyer, the Seller shall be entitled to require documented damages as of the fifth week of delay.

Art. 11.
OTHER PROVISIONS

11.1. Upon completion of the Object of the Agreement the Seller shall proceed with professional care. The Seller undertakes to comply with the generally binding legal regulations, technical norms and terms hereof.

11.2. The Object of the Agreement shall be owned by the Seller until the payment of the price.

11.3. The risk of damage to the Object of the Agreement shall be transferred to the Buyer upon compliance with Art. 7.

Art. 12.
FINAL PROVISIONS

12.1. The Agreement shall be executed immediately following delivery of final consent to the content of the draft Agreement to the other Party. The Agreement shall be executed by demonstrating the consent to all of its contents. The consent shall be in writing and signed by the authorized representative of the Party which demonstrated the same.

12.2. The text hereof may be changed or amended by written amendments only, which shall be valid if duly confirmed and signed by the authorized representatives of both Parties.

12.3. The Parties agree to express their opinions on the draft amendments hereto in writing and within 15 days following the delivery of the draft amendment to the other Party.

12.4. This Agreement shall be governed by the French law.

12.5. This Agreement has been executed in four copies, two of which shall be retained by the Seller and two by the Buyer.

for the Seller
in Paris on 14.05.2009

Jean-Marc David
Global Sales and Distribution Manager

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for the Buyer
in Paris on 14. 05. 2009

Prof. MUDr. Ján Štencl, CSc.
Chancellor

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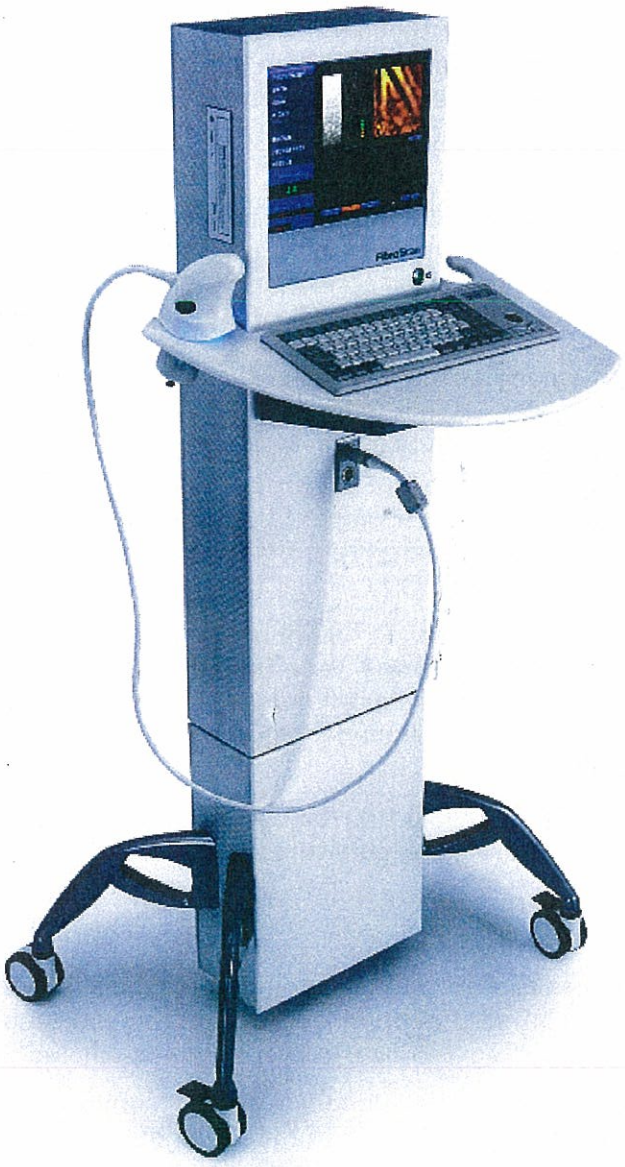
FibroScan®

HEPATIC FIBROSIS QUANTIFICATION BY MEASURING LIVER STIFFNESS



PRESENTATION FILE
NOVEMBER 2006

ECHOSENS

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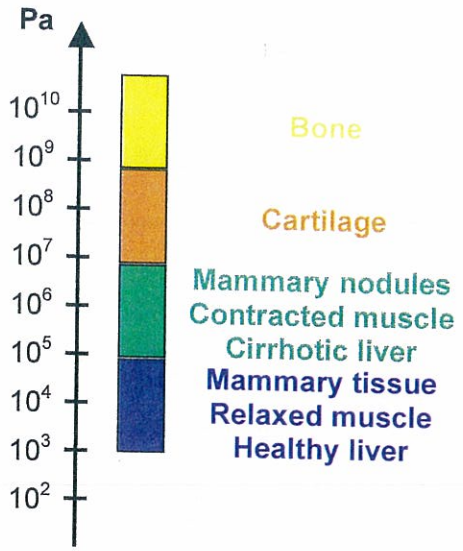


Figure 1. Examples of healthy and pathological tissue stiffness.

2. *What type of stiffness should be measured?*

The stiffness (E) refers to the ability of a medium to be deformed when subjected to mechanical stress. In physics, stiffness is generally represented by Young's modulus and expressed in Pascal (Pa).

When stress is applied to a medium, said medium may be deformed in two ways (Figure 2):

1. compression: the ability of the medium to be deformed by changing volume with the modulus in compression λ
2. shearing: the ability of the medium to be deformed without changing volume with the shear modulus μ

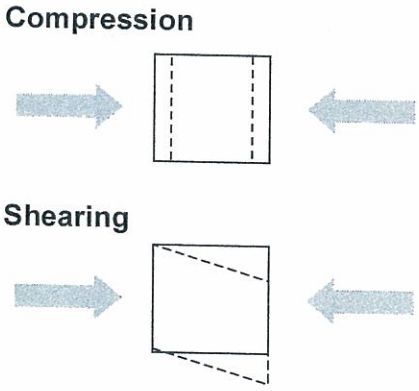


Figure 2: Medium compression and shearing

In a solid, the stiffness depends on both the modulus in compression λ and the shear modulus μ:

$$E = \mu\left(\frac{3\lambda + 2\mu}{\lambda + \mu}\right) \quad (1)$$

vivo as a function of the depth under the skin's surface and time (from the time that the measurement was activated).

The black areas correspond to positive deformation of the medium and the light areas to negative deformation. The black band through the image represents the deformations associated with the propagation of the shear wave, the penetration depth of which increases over time.

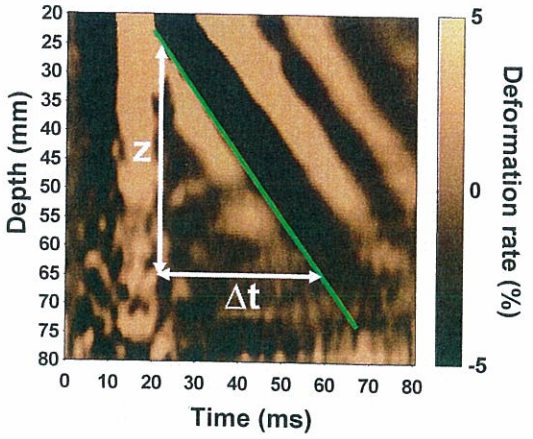


Figure 4. Image of deformation rates. The green line symbolises the propagation velocity of the elastic shear wave.

The measurement zone starts 25 mm under the skin so as to be under the liver capsule for most patients and extends over a depth z = 40 mm (Figure 4). The time (Δt) taken by the shear wave to propagate along the zone of interest is measured (Figure 4) and its propagation velocity is deduced:

$$V_S = z/\Delta t \,. \tag{4}$$

It is then possible to obtain the stiffness by combining the equations (2) and (3):

$$E = 3\rho V_S^2 \,. \tag{5}$$

The stiffer the medium is, the faster the propagation of the elastic shear wave is, meaning that Δt decreases and the slope of the black band (symbolised by the green line Figure 4) stiffens.

2. Software

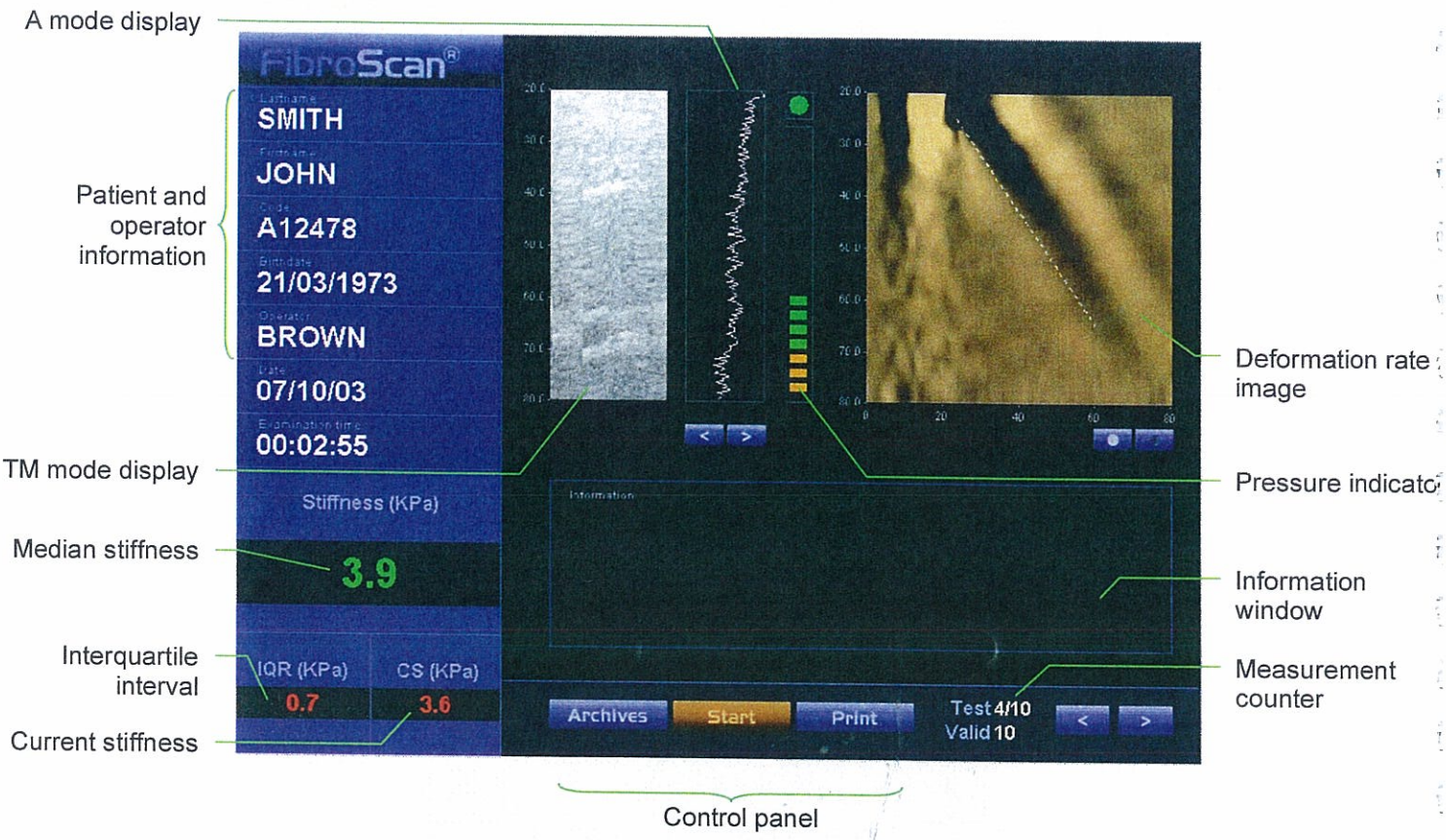


Figure 7. Software: hepatic stiffness measurement window.

The unit is controlled by a software program that can be used both to conduct hepatic stiffness measurement examinations and manage patient data. This software is loaded automatically when the unit is switched on. Figure 7 shows the software window during a patient examination.

As soon as the probe is in contact with a medium (when pressure is applied to the ultrasound transducer), the ultrasound acquisition is run. A mode display represents the amplitude of the envelope of the current ultrasound signal. The TM (time movement) display represents the envelope of ultrasound signals as a function of time encoded in greyscale.

Finally, the probe is equipped with a pressure sensor monitoring the pressure applied with the probe onto the patient's skin by the operator. The measurements from this sensor are displayed by the pressure indicator. When the pressure indicator level is in the orange zone, the pressure is not sufficient to activate measurement. If the pressure indicator level is in the red zone, the pressure is too high and an alert message notifies the operator. When the level is in the green zone, the pressure is then suitable to activate measurement.

The patient database can be used to sort and retrieve examinations using the patient's name, examination date or the operator's name.

For more information on the presentation of the unit, please refer to the user manual attached in appendix II.

F. PRECAUTIONS FOR USE

Only persons who have received training on the use of FibroScan® are authorised to conduct the liver stiffness measurement examination. **A half-day training session is essential for the proper use of the system and to obtain reliable and reproducible measurements.**

This examination is contraindicated for subjects with an active implantable device (such as a pacemaker, defibrillator, pump, etc.) and is not indicated in the absence of specific studies for children and pregnant women. Patient with ascites may not undergo this examination as the ascites fluid prevents the propagation of the elastic shear wave; however, this is not a genuine restriction given that the presence of ascites is sufficient to diagnose cirrhosis.

This medical device is a diagnostic aid. Only examinations consisting of 10 valid measurements can be interpreted and only by a liver disease specialist with knowledge of the patient's disease and its clinical context.

The threshold values presented in the literature must be used with care, accounting for the population from which they were obtained and the associated sensitivity and specificity values.

G. LIST OF PUBLICATIONS AND CONFERENCES

The list of publications and papers relating to FibroScan® is given in appendix IV.

pathologist; however, it has been demonstrated that there is a 10 to 20% between- and within-examiner variability for the evaluation of fibrosis[12]. These two points (the lack of representativeness of the sample and the variability of fibrosis evaluation) result in a false negative rate of 24% for cirrhosis screening[13].

The hepatic stiffness measurement examination is completely non-invasive and painless and requires no anaesthetic and, in particular, no hospitalisation. Therefore, it makes it possible to save the medical and nursing staff's time. The studies conducted have not demonstrated any side-effects or complications associated with the examination, which is also very well perceived and accepted by patients. Each measurement is made on a portion of liver representing a cylindrical specimen 1 cm in diameter and 4 cm long (Figure 10). Therefore, the stiffness measurement is 150 to 400 times more representative than NBL (length varying between 1 and 3 cm on average). Finally, this examination can be repeated as often as is necessary to monitor the progression of the disease with or without treatment.

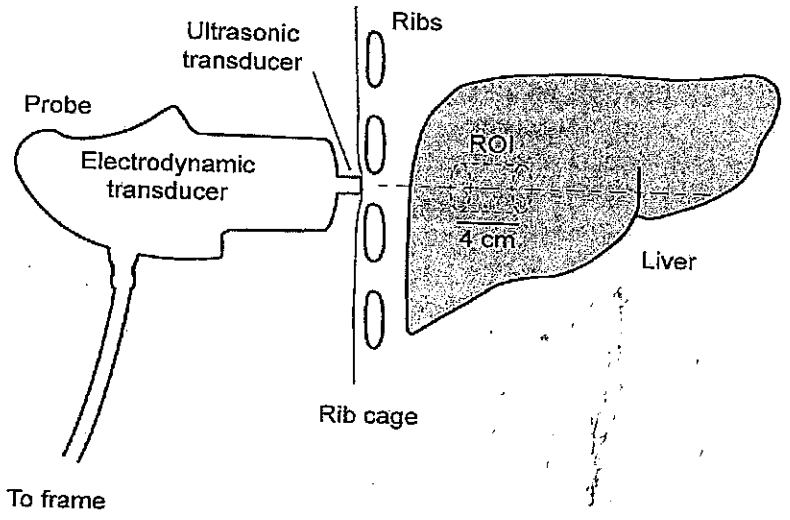


Figure 10. Hepatic parenchyma volume examined during a liver stiffness measurement with FibroScan®.

2. *Biological diagnosis (serum markers)*

Recently, a number of fibrosis markers or biochemical score systems were tested to replace NBL for hepatic fibrosis evaluation. These examinations simply require a blood sample, followed by an assay of the substances under test.

Fibrosis markers are produced by the synthesis or degradation of extracellular matrix proteins. Therefore, they are directly linked with fibrosis but not specifically with that of the liver. In fact, other organs such as the kidneys may develop fibrosis. In addition, these markers reflect dynamic processes (synthesis and degradation) rather than the quantity of fibrosis actually present.

Biochemical scores are combinations of serum parameters with an indirect relationship with hepatic fibrosis. These scores are constructed by means of statistical analysis so as to be as close to the results obtained with NBL as possible. In this way, these tests are very sensitive to blood parameter variations selected for reasons completely independent from fibrosis and the liver. Therefore, their use is restricted to specific and non-multiple underlying diseases (generally chronic hepatitis C virus). Similarly, some treatments also induce variations in some blood parameters included in these tests, so they cannot be used for the follow-up of patients under treatment.

III. STATUS OF EVALUATION IN HUMANS

A. REPRODUCIBILITY

The final result of a hepatic stiffness measurement examination consists of the median of 10 valid measurements. During a pilot study[3], the examination was repeated by the same operator and 3 times by three different operators on some fifteen patients. The between-operator variability (mean standardised coefficient of variation) is not more than 10% and changing the operator does not add variability to the result of the examination.

Additional studies are currently in progress in order to test the influence of different factors on the variability of the measurements.

B. CHRONIC HEPATITIS C

Chronic hepatitis C is currently the main reason for NBL. Therefore, the majority of the first FibroScan® evaluation studies related to this underlying disease.

1. Comparison with the METAVIR score (NBL)

The first studies[3,14-16] naturally consisted of comparing the hepatic stiffness measurement with the METAVIR[17] fibrosis score (F) evaluated using liver samples obtained by means of NBL.

The main multi-centre study[15] included 327 patients suffering from chronic hepatitis C with potential associated conditions (hepatitis B, alcohol, etc.). The histological slides were all read in double-blind mode by two anatomo-pathologists. Among these patients, 53 biopsies and 23 hepatic stiffness measurement examinations were considered as non-interpretable and were excluded from the statistical analysis.

Of the remaining 251 patients, the stiffness of the liver was significantly correlated with the METAVIR grade and independent, in a multivariate analysis, from the activity and steatosis. In addition, the diagnostic accuracy was estimated by calculating the area under the receiver-operator characteristic (ROC) curve in the following three cases:

- Screening for patients to be treated ($F \geq 2$)
- Screening for patients with severe fibrosis ($F \geq 3$)
- Screening for patients with cirrhosis ($F = 4$).

Similarly, in these three cases, liver stiffness threshold values were defined by optimising the sum of the sensitivity and the specificity. These results are compiled in Table 1.

	$F \geq 2$	$F \geq 3$	$F = 4$
Area under ROC curve	0.79	0.91	0.97
95% confidence interval	0.73 – 0.84	0.87 – 0.96	0.93 – 1.00
Threshold value (kPa)	8.74	9.56	15.52
Sensitivity	0.55	0.84	0.84
Specificity	0.84	0.85	0.94
Positive predictive value	0.87	0.71	0.76
Negative predictive value	0.51	0.93	0.96
Probability ratio	3.47	5.67	13.00

Table 1. Diagnostic accuracy and threshold values of FibroScan® in patients suffering from chronic hepatitis C[15].

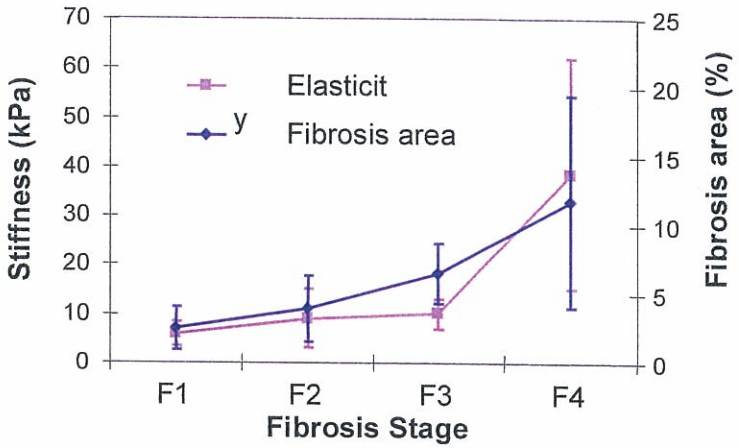


Figure 12. Liver stiffness and fibrosis area as a function of METAVIR fibrosis grade[18].

This preliminary study demonstrates that the stiffness of the liver measured by FibroScan® is correlated with the METAVIR fibrosis grade and also with the fibrosis area. In addition, the correlation between FibroScan® and the fibrosis area is greater than with the METAVIR grade. This could indicate that FibroScan® is a good reflection of the quantity of fibrosis present in the liver. An additional study on a large population is currently in progress on patients suffering from chronic liver disease of a variety of origins.

C. ALL UNDERLYING DISEASES

A prospective comparative study of hepatic fibrosis and hepatic stiffness was conducted on 514 patients suffering from chronic liver disease of a variety of origins (hepatitis B and/or C, HCV co-infection, HIV, alcoholism, non-alcoholic steato-hepatitis, haemochromatosis, etc.)[19]. The diagnostic accuracies of FibroScan® for the evaluation of fibrosis of all underlying diseases are given in Table 5.

	Moderate fibrosis or greater	Severe fibrosis or greater	Cirrhosis
Area under ROC curve	0.80	0.89	0.95
95% confidence interval	0.75 – 0.83	0.85 – 0.91	0.92 – 0.96

Table 5. Diagnostic accuracy of FibroScan® for all underlying diseases[19].

These results are identical to those obtained in patients suffering from chronic hepatitis C and suggest that FibroScan® can be used for the evaluation of hepatic fibrosis in patients suffering from the most commonly encountered forms of chronic liver disease in France.

D. CIRRHOSIS AND ITS COMPLICATIONS

The range of hepatic stiffness values in patients suffering from cirrhosis is very wide. Therefore, it is beneficial to study the potential relationship between the hepatic stiffness and

the severity of cirrhosis, particularly decompensation and the occurrence of complications such as oesophageal varices, splenomegaly, ascites or hepatocellular carcinoma (HCC).

1. Oesophageal varices

The purpose of the study by Kazemi *et al.*[20] was to compare the liver stiffness values with the presence and grade of oesophageal varices and the portal gradient in 166 patients with histologically proven cirrhosis with a C viral (n = 98), alcoholic (n = 35) or other (n = 33) underlying disease.

The correlation coefficients between the hepatic stiffness and the various parameters studied are presented in Table 6.

	FibroScan®
Child-Pugh score	0.42
Presence of oesophageal varices	0.60
Grade of varices	0.60
Blocked suprahepatic vein pressure	0.64
Portacaval gradient	0.64

Table 6. Correlation coefficients between hepatic stiffness and the various parameters studied ($p < 0.0001$)[20].

In addition, in patients having undergone a haemodynamic measurement, the stiffness of the liver had an improved diagnostic accuracy than the portacaval gradient (area under ROC curve of 0.89 and 0.78 respectively).

This study demonstrates that there is a relationship between the hepatic stiffness and the presence and size (or grade) of oesophageal varices and that it is correlated with the severity of the cirrhosis. Finally, a threshold value of 23 kPa made it possible to detect among cirrhotic patients those with very little likelihood of having grade II or II varices, i.e. at a risk of oesophageal haemorrhaging. Following confirmation with additional and independent studies, FibroScan® could be used to optimise planning of oesophageal varices screening endoscopic procedures which are expensive and not accepted well by patients.

2. Other complications

	r
Alanine amino transferase	0.190
Total bilirubin	0.466
Platelets	-0.429
Prothrombin time	-0.507
Albumin	-0.375
Child-Pugh score	0.544
Previous history of ascites	0.301
Grade II or III varices	0.343
Previous history of oesophageal haemorrhaging	0.273
Hepatocellular carcinoma	0.248
Splenomegaly	0.418

Table 7. Correlation coefficient (*r*) between hepatic stiffness and various factors[19].

miscellaneous (n = 12). The correlation coefficients of the hepatic stiffness and the FibroTest® value with the various parameters studied are given in Table 8.

	FibroScan®	FibroTest®
METAVIR fibrosis score	0.74 (0.001)	0.48 (NS)
Chevallier fibrosis score	0.71 (<0.0001)	0.54 (0.004)
Splenomegaly	0.63 (<0.0001)	0.38 (NS)
Hepatic dysmorphism	0.37 (0.05)	0.23 (NS)
Platelets	-0.57 (0.0004)	-0.14 (NS)

Table 8. Correlation coefficient (associated probability) between FibroScan® or FibroTest® and the various parameters studied[21].

These initial results obtained by modifying the measurement depth suggest that FibroScan® could also be used in children to evaluate hepatic fibrosis subject to adaptation. A specific probe for the morphology of young children is under development.

1. Technical description

CE 0459

Manufactured by: Echosens, SA
42, rue Monge
75005 Paris – France

Model: Fibroscan® 502

Power supply:
- 100 V (+10%/-15%) ~ 50–60 Hz
- 230 V (+10%/-15%) ~ 50–60 Hz

Usable power: 250 VA

Classification: Class I, type B 

Group I, Class B according to CISPR 11

IPX0: Apparatus not liquid-tight.

Function mode: Uninterrupted service with intermittent loading.

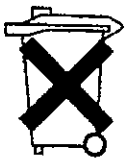
Loading time = $T_{loading}$ = 10 min.

Rest time = T_{rest} = 15 min.

Fuse: 4.0 AT (100 V), 2.0 AT (230 V)

- **Do not use in the presence of inflammable gases or anesthetics. An explosion could occur.**
- **Do not obstruct the vents.**
- **The chassis of the apparatus can only be opened by qualified maintenance personnel.**
- **Only qualified personnel authorized by Echosens® or its local representative, is authorized to repair the apparatus.**
- **Unpacking, assembly and transport of the apparatus must be carried out by qualified personnel.**
- **The apparatus can only be used with an SVGA screen that meets the IEC 950 §6.8.2j standard specifications.**

Battery disposal.



Fibroscan® uses a button lithium battery. Button lithium batteries are long-lasting batteries and it is possible that you may never need to replace it. However, if you need to replace it, do not throw the battery out with the regular garbage. Contact the municipal waste treatment service to find out the address of the battery deposit site nearest to you.

Size: 135 cm (height) x 68 cm (width) x 61 cm (depth).

echosens

Cena na základe špecifikácie
prístroja na vyšetrenie elasticity
parenchýmu pečene FibroScan 502
(Price based on the specification
of the instrument for investigation of elasticity
of the liver parenchyma FibroScan F502)

Por. (Number)	**Položka** (Item)	**Cena v Sk bez DPH** Price in euros without VAT	**DPH v Sk** VAT in SKK	**Cena spolu s DPH v Sk** Price including VAT in SKK
1.	FibroScan FS 502	63.000 euros		
2.	Dodanie, inštalácia (Delivery, installation)	4.000 euros (5.000 € minus exceptional discount of 1.000 euros)		
3.	Úvodné školenie (Initial training)	0 euros		
4.	Údržba (1 rok) (Maintenance (1 year))	5.190,94 euros		
5.	**SPOLU (TOTAL)**	**72.190,94 euros**		
6.	Pediatrická sonda S: (Paediatric probe S)	18.000 euros		
7.	**CENA SPOLU** (TOTAL)	90.190,94 euros		

(Kurz Národnej banky Slovenska platný v deň podania záväznej ponuky je rozhodujúci pre prepočet ceny v €.)
(Currency rate of the Slovak National Bank on the date of the submission of the offer is decisive for the exchange calculation of the price given in €.)