

Full Range of Tissue Microarrayers Instruments



Tissue & Cell Biotechnologies

Galileo AutoTiss 10c

Fully Automated Tissue Microarrayer

- **Fully Automated Control**
- **Digital Spot Identification**
- Excel format for import/Export clinical data
- Interface with Digital Scanners.
- Punch needle size: 0.6; 1.0; 1.5; 2.0 and 2.5 mm/dia.

Galileo TMA CK4500

Computer driven Tissue Microarray - Galileo TMA CKxxx:

- Open architecture: allows the use of different cassettes (standard, macro and mega (up to 80x120 mm) and 96 well plate formats (only on CK4500) for nucleic acids extractions (DNA-RNA and mRNA)
- Spot identification:
 - 1. Manual overlapping;
 - 2. Virtual overlapping with digital slide image and stretching function.

Galileo CK3500

- Excel Format for import/export clinical data, and XML Format to interface with Digital Scanners to keep traceability between donor and TMA spot.
- Interface with Digital Scanners: Aperio, Hamamatsu, TissueGnostics, others.
- Remote TMA preparation: allows to define the TMA geometry and design remotely.
- Wide needles selection: 0.6; 1.0; 1.5; 2.0; 3.0 and 5.0 mm/dia for standard and macro blocks.

Galileo CK25



- **Project base TMA creation**
- Replicate layout and clone TMA Blocks
- Custom recipient block design and production
- Custom rework for selected position on recipient block

Galileo AutoTiss One

Tissue Microarray (TMA)

"A Block Of Samples From Hundreds Of Blocks"
(S. M. Hewitt, M.D., Ph.D., Tissue Array Research Program, LP, CCR, NCI, NIH)



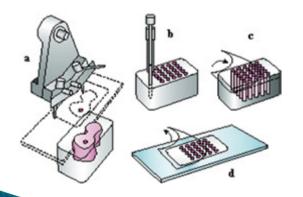
Tissue microarray technology

Multi-tissue blocks were first introduced by H. Battifora in 1986 with his so-called "multi-tumor (sausage) tissue block" and modified in 1990 with its improvement, "the checkerboard tissue block". In 1998, J. Kononen and collaborators developed the current technique, which uses a novel sampling approach to produce tissues of regular size and shape that can be more densely and precisely arrayed.

The TMA technology is a technical procedure that combines tens to hundreds of paraffin-embedded tissue specimens into a single paraffin block.

Cylindrical tissue cores (typically 0.6-2.0 mm in diameter) are acquired from one or more representative region(s) of a paraffinembedded tissue block (**donor block**) and then precisely arrayed into a new "**recipient**" **paraffin block**, using a custom-built instrument.

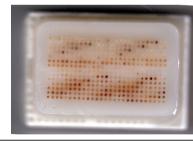
Up to 200 consecutive sections of 4-5µm thickness can be sliced from each TMA block, mounted on a microscope slide and processed like ordinary tissue sections with a wide range of techniques (histochemical staining, immunohistochemical and immunofluorescent staining, FISH).



TMA advantages

TMAs have a number of advantages compared with conventional techniques.

- •The speed of molecular analyses is increased by more than 100-fold,
- precious tissues are not destroyed
- •large number of molecular targets can be analyzed from consecutive TMA sections.





References:

- Battifora H: The multitumor (sausage) tissue block: novel method for immunohistochemical antibody testing. Lab Invest 1986, 55:244-248.
- Battifora H, Mehta P: The checkerboard tissue block. An improved multitissue control block. Lab Invest 1990, 63:722-724.
- Kononen J, Bubendorf L, Kallioniemi A, Barlund M, Schraml P, Leighton S, Torhorst J, Mihatsch MJ, Sauter G, Kallioniemi Tissue microarrays for high-throughput molecular profiling of tumor specimens. Nat Med 1998, 4:844-847.

Additional TMA applications

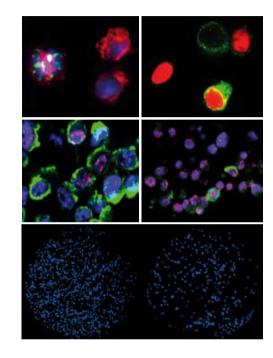
CELL MICROARRAY (CMA)

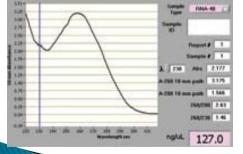
CMA evolved from TMA with the exception that fixed **cells are used instead of tissues**. Cells are grown in culture, suspended in agarose and embedded in paraffin.

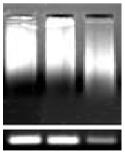
- Immunocytochemistry analysis (IC) of any type of cells
- High-throughput screening of hundreds of cell samples on a single slide
- Several slides can be generated from a paraffin recipient block ready to be assayed with different markers

TISSUE CORE PICKING & DISPENSING

- •Galileo 4500 can be used for TMA, CMA and as sample picker for nucleic acids (DNA and RNA) extraction and for protein isolation using appropriate fixative.
- •The tissue cores extracted from precise regions may be dispensed into dedicated vessels for further processing such as DNA, RNA, miRNA and protein extraction. Microfuge vials, strips or microtiter plates may be used, depending on the downstream applications. **Parallel analyses on the same specimen** can be performed simultaneously.







Nucleic Acids Extraction

- DNA extracted from tissue cores (1 mm size and 3.5 mm3) from human prostate, uterus and colon using silica based matrix (Malferrari et al., 2002).
- The agarose gel (0.8%) shows the quality of DNA extracted and the PCR amplification of the BRCA1 gene with specific primers

Galileo Auto Tissue Fully Automated Arrayer







Galileo AutoTiss 10C Technical features

- AutoTiss 10C: Patent No: US7,862,777B2 one of the most innovative invention.
- Compact and FULLY automated tissue microarrayer (TMA).
- Helps the researchers to decrease the time and labour in creating blocks.
- Capacity: 10 standard blocks at a time
- Punch needles: 0.6, 1.0, 1.5, 2.0, 2.5mm /Diam.
- TMA capacity : 504(28x18) with 0,6 punch, 200(20x10), 96(12x8), 54(9x6), 35(7x5) cores respectively
- Dimensions: 470 x 500 x 450 (WxDxH mm)



- Computer controlled, walk-away system: no more manual operation
- Graphical user friendly interface for easy operation
- Patented coaxial punch set and mechanism
- Patented CCD integration system for fast and easy punch area selection
- Block Database allow fast and easy tracking and maintainance



Galileo AutoTiss 10C Technical features

Hardware

Actuator Type :	Electromechanical
Repeatability:	+/- 0.01 mm / Axis
Resolution :	0.01mm / Axis
Motor System :	Micro step motor
Loading Method :	Rotary tray with universal loader
Control Method :	PC with Win 7-8.1 operating system
Lighting Method:	Halogen ring light illumination
CCD System :	High resolution CCD with auto focus module
Punching Method:	Patented coaxial punch module
Tray Capacity:	10 blocks per tray
Block Detection :	Auto height detection sensor
Heating Mechanism :	On/off Block Plate heater



Software

Database integrated with clinical and diagnosis data.

Parameter setting for customized arraying

CCD integration for advanced and easy punch area selection

Galileo CK Tissue Microarrayer Family



- Galileo CK3500Basic 6 Standard Blocks
- CCD Camera
- Interface with Digital Scanners
- Remote SW

- CCD Camera
- · Interface with Digital Scanners
- Remote SW

https://www.youtube.com/watch?v=X5nuTc GVf4





Galileo TMA CK4500 - CK3500: unique technical features

The only Tissue Array platform with an OPEN ARCHITECTURE which gives the possibility to work with :

1. Different size tissue paraffin blocks

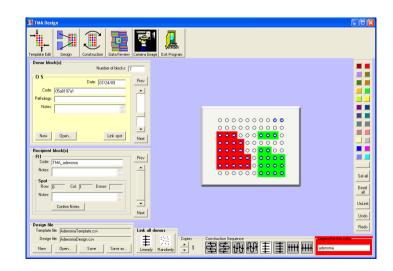
- •Possibility to work with the following configurations:
 - 9 standard tissue blocks which can be used independently as donor(s) or recipient tissue blocks (up to 8 replicas)
 - 3 standard blocks and 2 macro-blocks (macro block size: 55 x 45 mm)
 - 3 standard blocks and 1 custom size paraffin donor blocks (up to 120 x 85 mm).

2. 96 well plate format

•Possibility to dispense the tissue cores into dedicated vessels (96 well plates, strips, microfuge vials) for downstream application such as DNA,RNA and miRNA extraction.

USER FRIENDLY INTERFACE (isetma® software)

- •User friendly interface designed to assist the user in all TMA construction phases.
- ■The user interface has dedicated modules for: TMA geometry definition; TMA design, TMA construction and TMA reporting, which includes:
 - Generation of a report in Excel or in XML format to transfer TMA data to major digital scanners (e.g. Aperio, Hamamatsu, others).
 - Dedicated functions (manual or digital overlapping) for punch areas identification.
 - Specific function to manage "Pick & Dispense" the tissue cores in the 96 well plate or eppendorf vials.



The only Tissue Arrayer

- •CE marked for IVD applications
- •UL and CSA (...moving to MET) compliance

COVERED UNDER WORLDWIDE NIH LICENSE:

- •Tumor Tissue Microarrays for Rapid Molecular Profiling
- •US 6.699.710: AU 754.047: EP 1.068.528. CA 2.318.984

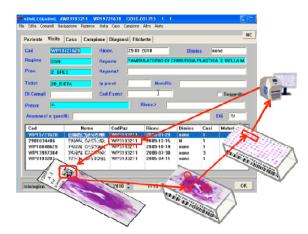
<u>Galileo TMA CK4500 - CK3500:</u> <u>additional features</u>

1D & 2D BARCODE TO ENSURE TOTAL TRACEABILITY

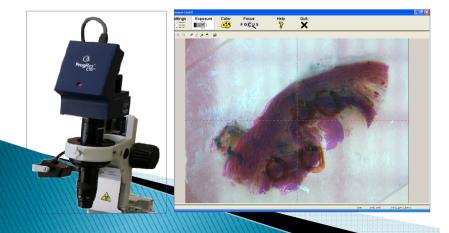
- Import the donor block codes that will be used in the TMA project.
- Check the donor block codes during the sampling phase to avoid mismatching that could compromise TMA quality.
- Define, import and check the tubes used during the "Pick & Dispense" operations

<u>HIGH-SPEED AUTOMATED TRAY WITH MODULAR TISSUE BLOCK</u> HOLDER

- Computer assisted and automated tray that ensures precise and rapid positioning of the paraffin blocks while in use.
- Modular sample holder that allows positioning of various specimen items: standard histological cassettes, macro-blocks, custom size paraffin blocks, microplates or microfuge vials.
- Dedicated holder designed according to microplate standard.
- Dedicated glass slide holders to capture digital images of both standard and macro glass slides.







HIGH RESOLUTION DIGITAL CAMERA

- Easy identification of the punch areas on the donor blocks. The operator looks at the images of the donor block and of the premarked reference slide on the PC monitor.
- Possibility to save the slides images and of the paraffin blocks on the computer HD for later use during virtual alignment in the punch area selection and for digital reports.

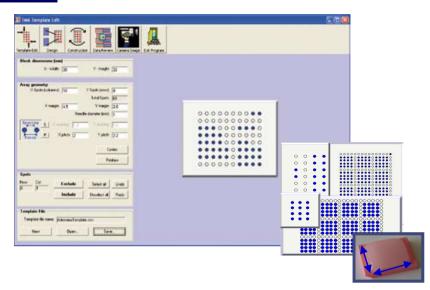
LED BACK-LIGHT AND REFLECTED ILLUMINATION

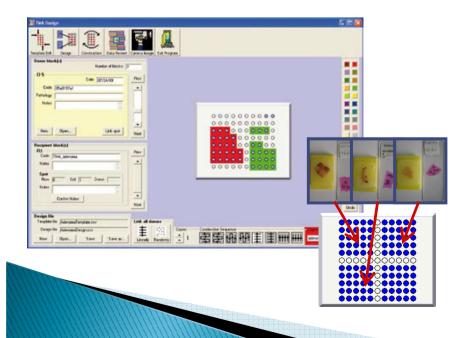
- Double source illumination of the paraffin blocks as well as the glass slides to improve the quality of the images.
- Independent regulation of the two light sources intensities.

The IseTMA® software

TEMPLATE EDIT

- Allows the creation of the geometry of the array (paraffin size, needle diameter, number of spots and spacing or pitch between the spots).
- · Automatic software check of data inconsistencies or errors.
- Introduce rows/columns or spot groups of spacing to separate the various specimens.
- · Automatically centre the array in the recipient block.
- Check the template directly on the recipient block
- Define a library of TMA templates (up to 99 templates) to be recalled and re-used in different TMA projects.





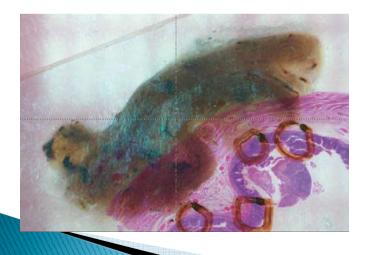
DESIGN

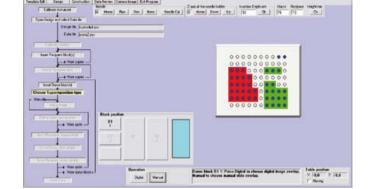
- Define the donor blocks to be used. Donor blocks can be inserted once or added during the work progression.
 - Import the donor block codes by using the barcode reader.
 - Import the donor block codes from an Excel list.
- Link each donor block to one or multiple spots of the TMA.
 - Manual spot link
 - Linear spot link
 - Random spot link
 - Automatic design creation
- Define up to 8 replicates (depending on the mounted configuration).
- Add a text note for each donor block, recipient block or spot.
 These notes will be copied in the final report.
- Associate a color code to each spot to improve TMA reading.

The IseTMA® software

CONSTRUCTION

- Follow the flow chart to proceed with the TMA construction.
- · Check the template directly on the recipient block.
- Save all the punch positions for each donor block at the same time. The arrayer will automatically place the blocks during the sampling.
- Check the donor blocks during the sampling phase to avoid mismatching.
- Advance from one step to the next with a simple click of the mouse. All the block movements are automatic.
- Adjust errors and position mismatches in any moment with dedicated functions.
- · Complete your array.





PUNCHING AREA SELECTION:

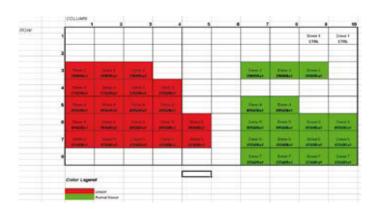
1. Manual overlapping:

- Sovraimpose the glass slide on the tissue block
- Align the pre-marked glass slide with the donor block by looking the zoomed images on the LCD color monitor.
- Capture (save) all punch positions using the joystick or with the mouse click.

2. Digital overlapping

- · Capture the glass slide image or import from a file
- Overlap the digitized pre-marked glass slide to the live block image adjusting the transparency as needed.
- Perfectly metch the glass slide image with the live block image (using the stretch image function)
- Capture (save) all punch positions using the joystick or with the mouse click.
- Include glass slide image into the digital report.

The IseTMA® software



INTERFACE WITH COMMERCIAL DIGITAL SCANNER FOR QUANTITATIVE DIGITAL PATHOLOGY ANALYSIS

- Create the final TMA report as standard XML TMA description file.
- Interface with other commercial digital scanners (e.g. Aperio, Hamamatsu, TissueGnostics and others)

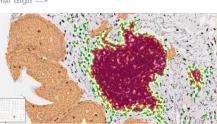
XML REPORT

- <!-- name of organization (from ini file) --> <contributor>ISE_strumento demo</contributor>
- <!-- block creation date --> <date>2011-12-21</date>
- <!-- name of this data file -->
- <filename>11T27CaColRout_rep.xml</filename>

</ri>

- <!-- ****** Common Data Elements (CDE) from TMA DES ****** -->
- <!-- number of this recipient block (alphanumeric) --> <block_identifier>11T27</block_identifier>
- <!-- notes for this recipient block -->
- <blook description/>
- <!-- template rows x columns (excluded spots counted also) -->
- <blook_number-of-cores>135</block_number-of-cores>
- <!-- needle diameter in mm with one decimal digit -->
-
<block_core-size>0.6</block_core-size>
- <!-- spot pitch, x and y direction, in mm with one decimal digit -->





DIGITAL REPORTING

Create the final report of the array on:

- Excel spread-sheet:
 - Each spot is properly identified during subsequent analysis.
 - Relate each spot to the corresponding information.
 - Personalize the report, for example adding the results of the analysis or images of the donor blocks and the spots.



<u>QUANTITATIVE DIGITAL PATHOLOGY</u> (TissueGnostics, Visiopharm)

- Automated and fast analysis of TMA cores or whole slides
- Accurate detection of tumor cells
- •Immediate deployment ensured with ready-to-run image analysis apps
- •Build your own image analysis protocols with highly flexible tools
- •Run as deployed analysis or pay-as-you-go with cloud analysis

CK3500 – CK4500 Technical Specifications

HIGH RESOLUTION OPTICS

- Optics: Navitar Zoom6000 modular lens system
- Jenoptik ProgRes SPEED XT Core 3 series
- CCD sensor: 1/1.8" 3.2 Megapixel Colour CCD (core 3)
- Pixel size: 3.45 µm2
- A/D Conversion: 3 × 12 bit RGB
- Image resolution: up to 2080 × 1542 pixels (17 fps)
- 42X magnification optic with a 21" wide display
- 48.8X magnification optic with a 24" wide display
- 54.9X magnification optic with a 27" wide display
- · Adjustable LED back-light and reflected-light illumination

AUTOMATED STAGE

- Prior Scientific ES111/H138 stage
- Modular sample holder to allow various specimen configuration

<u>NEEDLE HOLDER</u>

- Automated and computer guided needle positioning
- · Accurate user settings for the core insertion depth
- · Easy needle mounting

1D & 2D BARCODE READER

- •Handheld barcode reader to read barcodes on histological cassettes and vessels
- CCD digital scanning technology
- •Combined functionality: supports for all major 1D and 2D formats
- •Omni-directional scanning and wide working range to eliminate the need to align item and scanner
- Laser-generated aiming pattern to enable quick and accurate data capture

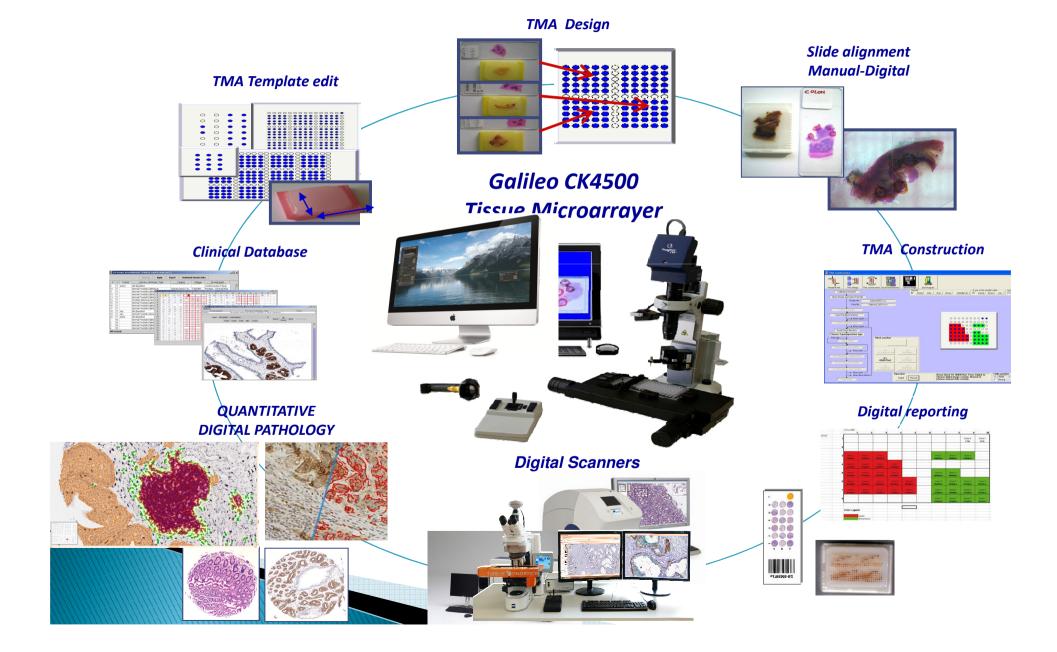
NEEDLES

- •Set of two punches: one for the donor block
- •Standard needles: 0.6-1.0-1.5 & 2.0 mm diameter for paraffin std block (up to 10mm sample depth)
- •Custom needles: 3.0 & 5.0 mm diameter (with special adapter) for paraffin std block (up to 10mm sample depth)
- •Macro needles: 1.0-1.5-2.0 mm diameter specially designed for paraffin macro-block (up to 15mm sample depth)

Technical Specification	CK2500	CK3500 Basic	CK3500 Advanced	CK4500
Standard Block Holder S = Standard M = Macro MP= 96 well plate or Custom (120x80 mm)	6 (S)	6 (S)	6 (S) 3 (S) + 1 (M)	9 (S) 6 (S) + 1 (M) 3 (S) + 2 (M) 3 (M) 6 (S) + 1 (MP)
Macro Block Holder			1	Up to 3
96 well plate format and/or Custom block				1
Barcode Reader		optional	optional	yes
Digital slide image for core selection		yes	yes	yes
Needle sizes 0.6 - 1.0 - 1.5 - 2.0 - 3.0 & 5.0 mm/dia.	yes	yes	yes	yes
Productivity	40 cores/h	60 cores/h	60 cores/h	90 cores/h



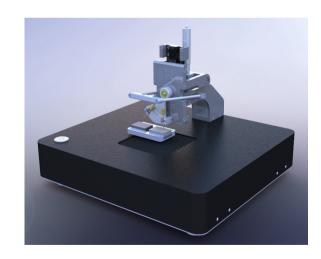
Tissue Microarray Pathology Platform Work-Flow



Semi-Automatic Arrayers Technical features



Galileo AutoTiss One



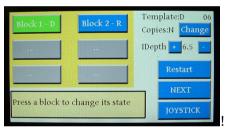
Galileo CK 2500

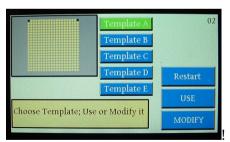
Semi-Automatic instrument:

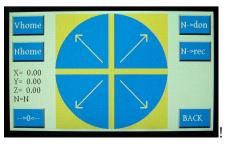
- Small footprint
- Touch screen panel
- Digital Joy-Stick
- Programming Capabilities
- Automated stage up to 6 tissue cassettes
- · automatic needles positioning
- Punching needles: 0.6-1.0-1.5 & 2.0 mm dia.











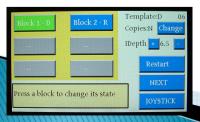
Galileo CK 2500





UP-TO-6 BLOCK AUTOMATED STAGE

- Computer assisted and automated tray that ensures precise and rapid positioning of the paraffin blocks while in use.
- Sample holder to position up to six standard histological cassettes
- Simple and flexible donor and recipient blocks positioning via touchkey panel



Tissue Arrayer characteristics

- Small foot-print (123 x 77 mm)
- Back lighting
- Needle sizes: 0,6, 1.0, 1.5 & 2.0 mm diameter

TOUCH PANEL user Interface

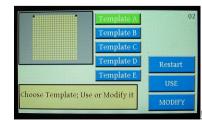
- Equipment interface designed to assist the user in all operating phases of the TMA project.
- Calibration
- Electronic Joy Stick
- Template Edit
- · Donor and receptor block selection
- Construction

AUTOMATED AND COMPUTER GUIDED NEEDLE POSITIONING

- Automated and computer guided needle positioning to help operator to construct the array, avoiding errors that could endanger TMA quality and speeds up the process.
- · Accurate and automated regulation of the core insertion depth.
- · Easy needle mounting.

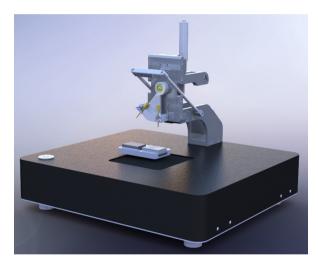
Template Edit

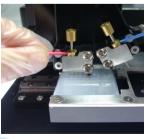
- Create geometry of the array (paraffin block size, needle diameter, number of spots and spacing or pitch between the spots).
- Introduce rows/columns or spot groups of spacing to separate the various specimens.
- Define a library of up to 5 TMA templates to be re-called and re-used in different TMA projects.



Galileo AutoTiss One Technical features

Auto Tiss One is a compact, hand carry <u>semi-automatic</u> tissue microarray (TMA) arrayer. A real cost-effective upgrade kit for manual TMA puncher.





Fully automatic planning, high throughput workflow

Computer controlled, no more manual positioning

Patent design graphical user interface for easy operation

Automatic for fast and easy punch area selection

Tissue database allow fast and easy tracking and maintenance

Operating system: Laptop Windows8

Total Weight: 8 kg

Dimensions : 405 x 350 x 424 (WxDxH mm)

Puncher size: 0.6, 1.0, 1.5, 2.0, 2.5 mm stainless needle Puncher

Stage Travel Range: 25,4 x 25,4 mm (1" x 1")

GALILEO TMA SERIES Technical Specifications										
Technical Characteristics	TMA Tiss-One	TMA CK 2500	TMA CK 3500 Basic	TMA CK 3500 Advanced	TMA CK 4500	TMA AutoTiss-10c				
SPECIMEN MOVEMENT	Semi-Automatic	Semi-Automatic	Automaticd computer- assisted	Automatic and computer- assisted	Automatic and computer- assisted	Fully Automatic				
Automated stage model		ISE engineered	Prior Scientific ES111 Optiscan Upright Stage	Prior Scientific ES111 Optiscan Upright Stage	Prior Scientific H138 stage					
Stage travel range	25,4 x 25,4 mm	123 x 77 mm	125 x 77 mm	125 x 77 mm	240 x 77 mm					
Stage speed	XY 100mm/s	1μm/s - 8mm/s	1μm/s - 8mm/s	1μm/s - 8mm/s	Up to 60 mm/s	XY:300 mm/s; Z:100 mm/s				
Repeatability	+/-10 μm/ Axis	5-7 μm	5-7 μm	5-7 μm	1-2 μm	+/-10 μm/ Axis				
Resolution	10 μm/ Axis	1 μm	1 μm	1 μm	To 0.01 μm	10 μm/ Axis				
USER INTERFACE	Tablet PC Windows8	Touch screen	User friendly dedicated	nd for picking & dispensing						
1D&2D Barcode reader	NO	NO	Optional	Optional	Included	Included				
Donor/Recipients positioning	Fixed	FREE	FREE	FREE	FREE	FREE				
MODULARITY OF THE SPECIMENT HOLDER	NO	NO	NO	LOW	HIGH	NO				
Standard Histological cassettes	1+1	Up to 6	Up to 6	Up to 6	Up to 9	Up to 10				
Macro blocks	NO	NO	NO	1	Up to 3	NO				
Custom size paraffin blocks	NO	NO	NO	NO	1 (up to 120 x 85 mm)	NO				
Microtiter plates	NO	NO	NO	NO	No	NO				
Microfuge vials (1.5-2.0 ml)	NO	NO	NO	Up to 12	Up to 14	NO				
Glass slides (standard and macro)	NO	NO	Optional	Optional	Included	NO				
CASSETTES BACKLIGHTING	NO	YES	YES	YES	YES	YES				
NEEDLES SIZE for Standard Blocks Standard Diameter	0.6 - 1.0 - 1.5 -2.0 - 2.5 mm	0.6-1.0-1.5-2.0 mm	0.6-1.0-1.5-2.0 mm	0.6-1.0-1.5-2.0 mm	0.6-1.0-1.5-2.0 mm	0.6 - 1.0 - 1.5 -2.0 - 2.5 mm				
NEEDLES SIZE for Standard Blocks (on request with special needle holder)		3.0 and 5.0 mm	3.0 and 5.0 mm	3.0 and 5.0 mm	3.0 and 5.0 mm					
NEEDLES SIZE for Macro Blocks	Macro not available	Macro not available	Macro not available up-gradable	1.0-1.5-2.0 mm diameter	1.0-1.5-2.0 mm diameter	Macro not available				
Core punching										
Needle positioning	Manual	Automatic	Automatic and computer-assisted			Automatic				
Regulation of the core insertion depth	N/A	Manual	Manual	Manual	Manual	Automatic				
Punch area selection	Visual selection Glass	Slide matching	High resolution optics (Jenoptik ProgRes SpeedXT Core 3 CCD Camera) for easy identification of the punch areas on the donor blocks			13 Mega Pixel Hi-Res Camera with Autofocus				
Core Selection	Manual	Manual	Dedicated SW functions	ng block and slide images.						
Throughput (cores/hour)	10	40	60	60	90	150				
Bench space required (cm)	40x35x60	32x50x60	75x160x80	75x160x80	75x180x80	75x180x80				
Weight (kg)	5	12	35	40	55	55				



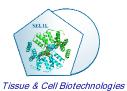
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 $e.mail: \ \underline{info@isenet-usa.com} \ -web: \underline{www.isenet-usa.com}$

REVENUE ID: 1000453540 - EIN: 46-1766310



Main Office Europe:

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