



RANDOX

Biochip Array Technology explained

The 'Gold Standard' in multiplex testing



Biochip Background

Established in 1982, Randox is a market leader in the field of high quality diagnostic solutions. With origins in clinical chemistry, Randox adapted its expertise and product range to include immunoassays, quality management and life science solutions. Randox's vision is to develop innovative and clinically meaningful diagnostics, ultimately improving laboratory testing and healthcare solutions worldwide.

Approximately 2% of all healthcare costs are diagnostics; however, 70-80% of all clinical decisions are based on the results of diagnostic tests. Traditionally six or seven single analyte diagnostic tests were carried out individually for each patient diagnosis resulting in time consuming and costly laboratory analysis. Moreover, this was not enough information to gain an accurate picture for diagnosis.

In 1992, Randox created a concept that would transform laboratory testing – Biochip Array Technology (BAT). The aim of this technology is to provide clinicians with as much patient information as possible, faster and more efficiently than traditional methods. An astonishing £180 million investment by Randox on research and development and a persistent strategy of innovation allowed Biochip Array Technology to evolve.

To date this technology has transformed diagnostics worldwide, saving time and money within the laboratory and allowing for highly accurate and informed clinical decisions. Randox continues to re-invest in the development of biochip arrays, with the goal of making a significant difference to diagnostics worldwide.

Applications

Since its inception, Biochip Array Technology applications have significantly evolved with a wide range of novel and routine assays. Biochip arrays are suitable for use in a wide range of settings including:

- Clinical laboratories
- Research laboratories
- Forensic and clinical toxicology
- Hospital laboratories
- Veterinary laboratories

The Technology Explained

Put simply, Biochip Array Technology is a multi-analyte testing platform allowing the simultaneous quantitative or qualitative detection of a wide range of analytes from a single sample. It provides a unique platform for assessment of biological samples in a rapid, accurate and easy to use format.

The problem with traditional diagnosis

Traditional diagnosis takes the form of single analyte assays, even though several tests are usually required. This may result in multiple patient blood draws, increased reagent volume, ultimately increasing time to diagnosis.

The solution

In response, Randox created Biochip Array Technology and the Evidence analyser as a solution. Simultaneous detection of multiple analytes produces a complete patient profile, providing exceptional time, resource and cost savings.

THE BIOCHIP - THE FOUNDATION OF BIOCHIP ARRAY TECHNOLOGY

- A 9x9mm biochip acts as the solid phase and as the reaction vessel, replacing multiple cuvettes
- Biochips are pre-fabricated with an array of discrete test regions (DTRs) with a different test located at each DTR
- One biochip is used per sample to produce multiple test results simultaneously
- Randox Biochips currently hold up to 49 tests, with the potential to significantly increase this number

The biochip surface

The surface of the biochip is chemically coated using a proprietary silanation process which allows for:

- Activation of the biochip surface – ensuring uniformity and reproducibility, minimising batch to batch variations
- Modification of surface chemistry during the activation process – controlled binding of antibodies in optimal orientation

Control sites – ensuring reliable IQC

Each Biochip contains internal quality control sites, which are always on the same position on every biochip. The control DTRs have set target levels in order to identify problems. If the levels for these control DTRs fall outside specified target ranges, an error code will be generated instead of a result, indicating an inaccurate result.



Biochip (9x9mm)

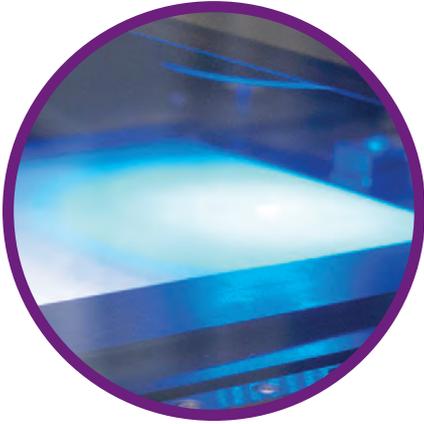


Biochip carrier

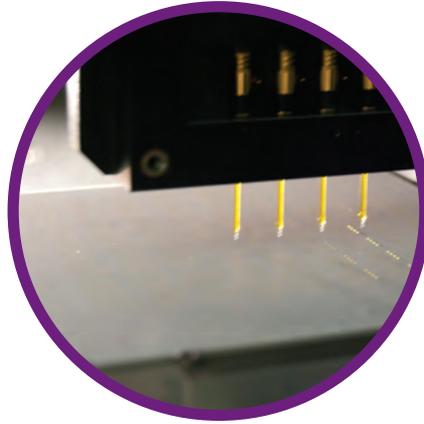


Fully automated Evidence Evolution biochip analyser

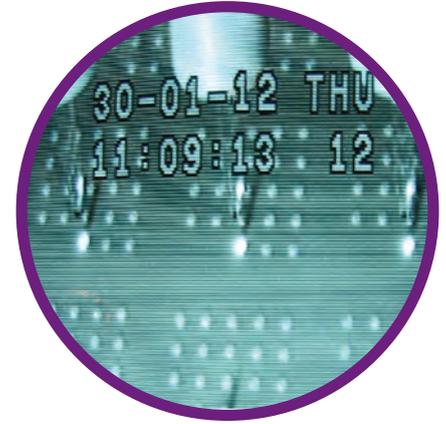
Production of the Biochip



Biochip sheets ready for spotting



Formatting equipment delivers the droplets of antibody



A camera takes an image of every biochip

PRODUCTION OF THE BIOCHIP

Many years of development and the expertise of highly qualified scientists have gone into the creation of the Biochip. We have integrated various different innovative technologies into the biochip production process. Some of which include:

- **Synthetic chemistry** - In order to develop novel biological ligands
- **Nano-dispensing** - The physical process of placing the binding ligands on the discrete test regions
- **Detection technology** - The development of a suitably sensitive detection technology

THE MANUFACTURING PROCESS

Each Biochip is manufactured under the strictest quality control procedures. Randox established the world's first protein Biochip manufacturing facility at their UK headquarters. This innovative facility includes state-of-the-art equipment specifically designed for the Biochip production process. A 10,000 class clean room has the capacity to produce 20 million Biochips per year at this location. Following this, Randox developed a new manufacturing facility in the USA in order to increase manufacturing capacity and meet the growing demand for Biochips globally.

Machinery within our clean room fully automates the production process, eliminating the risk of human error and speeding up the entire production process. This enables a very high production rate, which is required to meet demand for this technology.

QUALITY CONTROL

Quality is a top priority at Randox throughout our entire product range. The process of ensuring high standards begins at the research stage and is continued into manufacturing, therefore producing a final product that is of the highest quality standard.

The technology employed in manufacturing the Biochip incorporates a Quality Control Inspection System. Randox has developed this new software in-house. A photographic image is taken of each Biochip which records the dimensions of each DTR and then passes or rejects each biochip on an individual basis.

The Biochips are then cut from the sheets and assembled into the Biochip carriers in the purpose built automated assembly unit. The temperature and humidity is carefully controlled in the clean room to eliminate contamination, another important quality control feature. This extensive and thorough QC inspection ensures every single Biochip is completed to the same high quality standard.

ASSAY FORMATS

Protein / Antibody assay formats

Competitive immunoassay

In a competitive immunoassay, the more analyte present in a sample, the less labelled conjugate that will bind to the immunoreaction site. Therefore the signal produced will be low. If there is little analyte in the sample, more labelled conjugate will bind to the capture antibody resulting in a higher signal.

Sandwich immunoassay

In a sandwich immunoassay, the more analyte present in a sample, the more conjugate will bind to the capture antibody. As a result, the signal will be high. Conversely, lower signal is produced when the concentration of analyte in the sample is low.

Antibody Capture

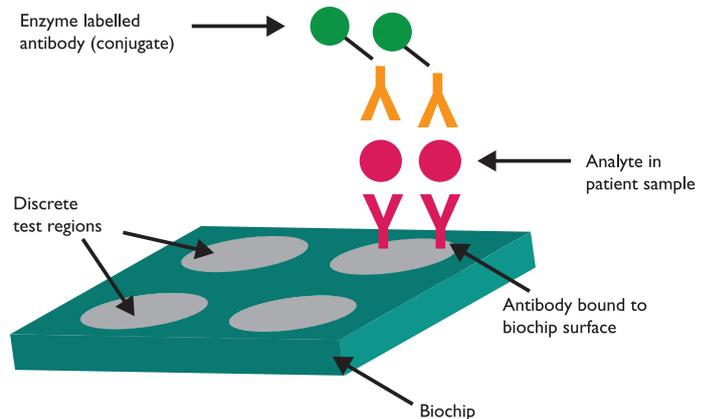
In this methodology antigens are prefabricated onto the surface of the biochip and antibodies in the sample are then bound.

SNP Genotyping

Rapid, multiplex SNP genotyping is based on innovative primer design which can discriminate sequences which differ only at one base. Products amplified therefore, will correspond to target portions of DNA from tissue, buccal swabs or blood. Amplified regions are then hybridised to a biochip array with spatially tethered probes complementary to target amplicons. Each array position corresponds to a specific SNP genotype and therefore is capable of both multiplexing and determining the zygosity of the sample.

Gene Expression

Individual genes are differentially expressed according to internal and external cellular inputs. Interpretation of the expression levels of one or a number of genes can provide valuable information relating to the physiological health of a cell or associated organ in an individual at that time. Harnessing such gene expression or gene signatures, particularly in a multiplex array, can provide a powerful insight into normal and disease processes. Randox has taken advantage of advances in amplification technology and biochip arrays to create a number of quantitative RNA expression arrays that will enhance clinical decisions and therapy choice, leading to more personalised care for each patient.



Pathogen Detection

Pathogen detection via nucleic acid (DNA/RNA) analysis offers rapid, sensitive, multiplex detection of viral, bacterial and protozoan pathogens. Following nucleic acid extraction from a broad range of sample types (sputum, urine, swabs etc) target DNA/cDNA is amplified in a single reaction and subsequently hybridised to a biochip array containing up to 23 pathogen-specific probes. This rapid, highly sensitive and specific process enables identification of primary and co-infections simultaneously, often in asymptomatic patients and has the capacity for use with many pathogen panels.

Mutation Detection I

These rapid mutation profiling arrays, consist of highly multiplexed mutation PCRs coupled to hybridisation of amplicons to spatially tethered probes on a biochip array. Each array position corresponds to a specific mutation/probe combination, allowing numerous targets to be analysed simultaneously. This assay has the advantage of speed, ease of use and the ability to quickly identify multiple mutations from a single sample.

The art of detection - perfected

The biochip detection system is based on a chemiluminescent signal. This is the emission of light, without heat, as a result of a chemical reaction.

An enzyme is used to catalyse the chemical reaction on the biochip which generates the chemiluminescent signal. The light emitted from the chemiluminescent reaction that takes place in each DTR is simultaneously detected and quantified using a Charge - Coupled Device (CCD) Camera. This CCD Camera simultaneously records the light emission from all the discrete test sites on each biochip on the biochip carrier.



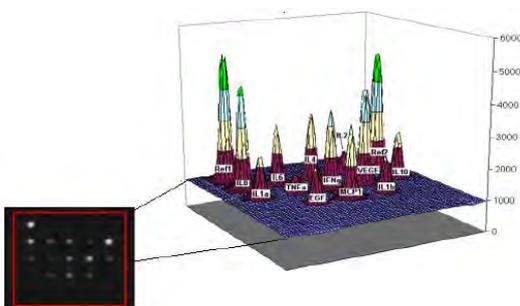
Analysis process on biochip systems



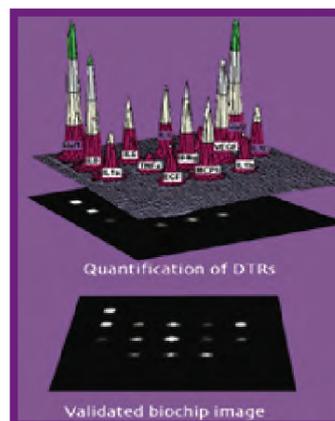
1. Unique imaging software on the analysers is used to translate the light signal into an analyte concentration.



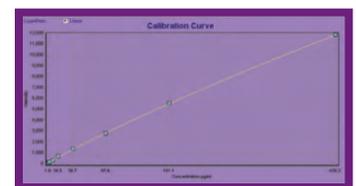
2. The CCD Camera is made up of a collection of light sensitive diodes which convert light into electrons to produce an electrical charge. The brighter the light that hits a single diode, the greater the electrical charge that will accumulate at that site.



3. The degree of light emission can therefore be quantified based on the strength of the electrical signal generated.



4. A validated biochip image is then produced, which undergoes image analysis for quantification of the signal output at each DTR.



5. A validated calibration curve is used to determine the concentration of each analyte.

The art of detection - perfected

Key Features and Benefits

Highly accurate testing

- BAT has a proven high standard of accurate test results with CV's <10%
- Multiplex analysis minimises analytical variation between tests

Better patient diagnosis

- Testing for multiple markers simultaneously increases the amount of patient information rapidly available to the clinician, allowing for more informed patient diagnosis

Optimum efficiency

- Multi-analyte reagents and quality control material, provides highly efficient testing while eliminating any wastage

Small sample volume

- Reduced sample volume requirements puts the patient at ease
- Patient profiling saves precious sample if further analysis is required

Cost consolidation

- Multiplex testing reduces the amount of time spent on individual tests and associated laboratory costs

Wide and varied test menu

- Randox's vast Biochip test menu allows clinicians to detect routine and novel markers for advanced diagnostic analysis

Extensive quality control features

- Internal quality control markers on every biochip ensure optimum assay performance
- Comprehensive Quality Control data is automatically created and displayed with every patient result

Multiple sample types

- Multiple sample types can be used on one analyser including serum, plasma, whole blood, urine, oral fluid and alternative matrices
- This allows the clinician to offer flexible patient testing

Result traceability

- Bar-coded biochips and patient samples ensure complete traceability of results

Retrospective reporting

- Retrieve previously unreported results without additional testing, saving time

Biochip Test Menu

Clinical Arrays

Cardiac Array

Creatine-Kinase Muscle Brain (CK-MB)
Heart Type Fatty Acid Binding Protein (H-FABP)
Myoglobin(Myo)
Troponin I (cTnl)

Thyroid Total Array

Thyroid Stimulating Hormone (TSH)
Total Thyroxine (TT4)
Total Tri-iodothyronine (TT3)

Fertility Hormone Array

Estradiol (EST)
Follicle Stimulating Hormone (FSH)
Luteinising Hormone (LH)
Progesterone (PROG)
Prolactin (PRL)
Testosterone (TEST)

Vitamin D Array*

Vitamin D (VITD)

Thyroid Free Array

Free Thyroxine (FT4)
Free Tri-iodothyronine (FT3)
Thyroid Stimulating Hormone (TSH)

Tumour PSA Array

Carcinoembryonic Antigen (CEA)
Free Prostate Specific Antigen (fPSA)
Total Prostate Specific Antigen (tPSA)

*Applications available for serum and/or plasma
* Coming soon for Investigator only*

Research Arrays

Adhesion Molecules Array

E-Selectin
L-Selectin
P-Selectin
Intercellular Adhesion Molecule-1 (ICAM-1)
Vascular Cell Adhesion Molecule-1 (VCAM-1)

Cerebral Array I

Brain-Derived Neurotrophic Factor (BDNF)
Glial Fibrillary Acidic Protein (GFAP)
Heart Type Fatty Acid Binding Protein (H-FABP)
Interleukin-6 (IL-6)

Cerebral Array II

C-Reactive Protein (CRP)
D-dimer
Neuron Specific Enolase (NSE)
Neutrophil Gelatinase-Associated Lipocalin (NGAL)
Soluble Tumour Necrosis Factor Receptor I (sTNFRI)

Cytokine Array I

Epidermal Growth Factor (EGF)
Interferon- γ (IFN- γ)
Interleukin-1 α (IL-1 α)
Interleukin-1 β (IL-1 β)
Interleukin-2 (IL-2)
Interleukin-4 (IL-4)
Interleukin-6 (IL-6)
Interleukin-8 (IL-8)
Interleukin-10 (IL-10)
Monocyte Chemotactic Protein-1 (MCP-1)
Tumour Necrosis Factor- α (TNF- α)
Vascular Endothelial Growth Factor (VEGF)
(High sensitivity Array on Evidence Investigator only)

Cytokine Array II

Eotaxin
Insulin like Growth Factor 1, Free (IGF-1 (free))
Interleukin-1 Receptor Antagonist (IL-1Ra)
Interleukin 12/23 p40 (IL12/IL23-p40)
Interferon- γ -Inducible Protein 10 (IP-10)
Platelet Derived Growth Factor BB (PDGF-BB)
Regulated on Activation, Normal T Expressed and Secreted (RANTES)

Cytokine Array III

Granulocyte Macrophage Colony Stimulating Factor (GM-CSF)
Interleukin-5 (IL-5)
Interleukin-15 (IL-15)
Macrophage Inflammatory Protein-1 α (MIP-1 α)

Cytokine Array IV

Matrix Metalloproteinase-9 (MMP-9)
Soluble IL-2 Receptor α (sIL-2R α)
Soluble IL-6 Receptor (sIL-6R)
Soluble Tumour Necrosis Factor Receptor I (sTNFRI)
Soluble Tumour Necrosis Factor Receptor II (sTNFRII)

Cytokine Array V (On Evidence Investigator only)

Interleukin-3 (IL-3)
Interleukin-7 (IL-7)
Interleukin-13 (IL-13)
Interleukin-12p70 (IL-12p70)
Interleukin-23 (IL-23)

Endocrine Array

Cortisol
Dehydroepiandrosterone Sulphate (DHEAs)
Leptin
17 α Hydroxyprogesterone

Metabolic Syndrome Array I

C-peptide
Ferritin
Insulin
Interleukin-1 α (IL-1 α)
Interleukin-6 (IL-6)
Leptin
Plasminogen Activator Inhibitor-1 (PAI-1)
Resistin
Tumour Necrosis Factor- α (TNF α)

Metabolic Syndrome Array II

Adiponectin
C-Reactive Protein (CRP)
Cystatin C

Applications available for serum and/or plasma

Molecular Arrays available on Evidence Investigator only

Respiratory Multiplex Array

Influenza A
Influenza B
Human adenovirus B/C/E
Human bocavirus 1/2/3
Human coronavirus 229E/NL63
Human coronavirus OC43/HKU1
Human enterovirus A/B/C
Human metapneumovirus
Human parainfluenza virus 1
Human parainfluenza virus 2
Human parainfluenza virus 3
Human parainfluenza virus 4

Human respiratory syncytial virus A
Human respiratory syncytial virus B
Human rhinovirus A/B
Chlamydomphila pneumoniae
Haemophilus influenza
Legionella pneumophila
Moraxella catarrhalis
Mycoplasma pneumoniae
Staphylococcus aureus
Streptococcus pneumoniae

STI Array

Chlamydia trachomatis
Neisseria gonorrhoea
Herpes simplex I
Herpes simplex II
Treponema pallidum
Trichomonas vaginalis
Mycoplasma hominis
Mycoplasma genitalium
Ureaplasma urealyticum
Haemophilus ducreyi

K-RAS/BRAF/PIK3CA Array

K-RAS
BRAF
PIK3CA

Cardiac Risk Prediction Array

Familial Hypercholesterolemia Array

Applications for a wide range of matrices

Toxicology Arrays

Drugs of Abuse Array I Plus

Amphetamine
Barbiturates
Benzodiazepine I
Benzodiazepine 2
Buprenorphine
Cannabinoids
Cocaine metabolite (Benzoylecgonine)
MDMA
Methadone
Methamphetamine
Opiates
Phencyclidine
Tricyclic Antidepressants (TCAs Generic)

Drugs of Abuse Array II

Buprenorphine
Fentanyl
Generic Opioids
Ketamine
LSD
Methaqualone
MDMA
Oxycodone 1
Oxycodone 2
Propoxyphene

Drugs of Abuse Array III

Chloral Hydrate Metabolite
Ethyl Glucuronide
Fentanyl
Ketamine Metabolite
Meperidine
Meprobamate
Zaleplon
Zolpidem
Zopiclone
Flunitrazepam

Drugs of Abuse Array IV

Acetaminophen
Dextromethorphan
Escitalopram
Ethyl Glucuronide
Fluoxetine
Haloperidol
Ibuprofen
Methylphenidate
Salicylate
Sertraline
Tramadol
Trazodone
Tricyclic Antidepressants (TCAs Generic)

Drugs of Abuse Array V

Bath Salts I (Methcathinone + Mephedrone)
Bath Salts II (MDPV)
Benzylpiperazines
Mescaline
Phenylpiperazines I
Phenylpiperazines II
Salvinorin
Synthetic Cannabinoids I
Synthetic Cannabinoids II
Synthetic Cannabinoids III
Synthetic Cannabinoids IV

Drugs of Abuse Array VI

Meprobamate
Zopiclone
Zaleplon
Zolpidem

Applications available for urine, whole blood, oral fluid and a wide range of forensic matrices.

(For urine applications creatinine is included as a dilution marker)

Food Diagnostics Arrays available on Evidence Investigator only

Anthelmintics Array

Benzimidazoles
Aminobenzimidazoles
Thiabendazole
Tricladendazole
Avermectins
Moxidectin
Levamisole

Athelmintics Array

Avermectins only

Anti-Microbial Array I Plus

Sulphachlorpyridazine
Sulphadiazine
Sulphadimethoxine
Sulphadoxine
Sulphamerazine
Sulphamethazine
Sulphamethizole
Sulphamethoxazole
Sulphamethoxyypyridazine
Sulphamonomethoxine
Sulphapyridine
Sulphaquinoxaline
Sulphathiazole
Sulphisoxazole
Trimethoprim

Anti-Microbial Array II

Ceftiofur
Quinolones
Thiamphenicol
Streptomycin
Tetracyclines
Tylosin

Anti-Microbial Array III

AHD
AMOZ
AOZ
Chloramphenicol
SEM
Chloramphenicol Glucuronide

Anti-Microbial Array III (Chloramphenicol only)

Chloramphenicol
Chloramphenicol Glucuronide

Anti-Microbial Array IV

Amikacin / Kanamycin
Apramycin
Bacitracin
Erythromycin
Lincosamides
Neomycin / Paromomycin
Spectinomycin
Spiramycin / Josamycin
Streptomycin / Dihydrostreptomycin
Tobramycin
Tylosin / Tilimicosin
Virginiamycin

Beta Lactam Antibiotics Array Plus

Ampicillin
Amoxicillin
Cefacetil
Cefazolin
Cefoperazone
Cefquinome
Ceftiofur
Cefuroxime
Cephalexin
Cephalonium

Cephapirin
Cloxacillin
Dicloxacillin
Nafcillin
Oxacillin
Penicillin G
Penicillin V

Beta Lactam Antibiotics Array

Ampicillin
Amoxicillin
Cefacetril
Cefazolin
Cefoperazone
Cefquinome
Ceftiofur
Cephalexin
Cephalonium
Cephapirin
Cloxacillin
Dicloxacillin
Nafcillin
Oxacillin
Penicillin G
Penicillin V

Beta Agonist Array

Zilpaterol only

Coccidiostats Array

Clopidol
Decoquinatone
Diclazuril
Halofuginone
Imidocarb
Lasalocid
Maduramicin
Monensin

Nicarbazin
Robenidine
Salinomycin / Narasin
Toltrazuril

Growth Promoter Multiple Matrix Screen Array

β -agonists
Boldenone
Corticosteroids
Nandrolone
Ractopamine
Stanozolol
Stilbenes
Trenbolone
Zeranol

Growth Promoter Multiple Matrix Screen

Ractopamine only

Growth Promoter Rapid Urine Screen Array

β -agonists
Boldenone
Corticosteroids
Ractopamine
Stanozolol
Trenbolone
Zeranol

Synthetic Steroids Array

Ethinylestradiol
Gestagens
Methyltestosterone
17 β - Clostebol

Applications available for feed, honey, milk, urine, tissue, egg, seafood

Biochip Test Platforms

—evidence— EVOLUTION



- Fully automated, floor standing
- Up to 2700 tests per hour
- Random Access
- Ideal for STAT samples
- Multiple tests from 7µl sample
- Sample matrices include plasma, serum, whole blood
- Capacity for 200 biochips onboard
- Barcode scanner for sample traceability
- Bar-coded samples and RFID-tagged reagents
- Applicable for all standard collection tubes
- Robust Bio-drive robotics
- Integrated Graphical User Interface
- Automatic software update via internet
- Probe liquid level, clot and bubble detection
- Real time data filtering and reporting
- User-defined cut-off levels without recalibration
- Extensive QC data generation
- Touch screen monitor
- Internal back-up stores over 2 years of results
- Retrospective reporting
- Password protected GUI
- Automatic disposal of biochips
- Chain of custody features
- Suitable for high throughput laboratories
- Onboard refrigeration of reagents

Biochip Test Platforms

evidence

- Fully automated, floor standing
- Up to 1980 tests per hour
- Multiple tests from 7 μ l sample
- Barcode scanner for sample traceability
- Bar-coded samples and reagents
- Internal back-up stores over 6 years of results
- User-defined cut-off levels without recalibration
- Extensive QC data generation
- Retrospective reporting
- Password protected GUI
- Automatic disposal of biochips
- Chain of custody features
- Suitable for high throughput laboratories
- Onboard refrigeration of reagents



— evidence — INVESTIGATOR



- Semi-automated, bench-top
- Up to 702 tests in 70 minutes
- Multiple tests from 25 μ l sample
- Ability to store and retrieve work lists saving time
- Barcode scanner for sample traceability
- Bar-coded samples and reagents
- Internal back-up stores over 6 years of results
- User-defined cut-off levels without recalibration
- Extensive QC data generation
- Retrospective reporting
- Password Protected GUI
- Chain of custody features
- Suitable for medium throughput laboratories

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