

RANDOX

BIOCHIP TECHNOLOGY EXPLAINED



GOLD STANDARD IN MULTIPLEX TESTING

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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 2002, 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 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 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
- Molecular Laboratories
- Veterinary laboratories
- Near patient testing
- Food diagnostics



THE TECHNOLOGY EXPLAINED

Put simply, Biochip 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 BIOCHIP - THE FOUNDATION OF THE TECHNOLOGY

In response, Randox created Biochip 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.

- A biochip is a 9 x 9 mm square-shaped solid substrate.
- 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 have up to 49 DTRs, with the potential to significantly increase this number

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

Each Biochip contains internal quality control sites, which are always in 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 a fault.

PRODUCTION OF THE BIOCHIP

Many years of development and 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 Donegal, Ireland 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. This software ensures that 100% of manufactured biochips are inspected to ensure our quality standards are met.

The Biochips are then cut from the sheets and assembled into the Biochip carriers in the purpose built automated assembly unit. The cleanroom environment and air handling eliminates 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

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

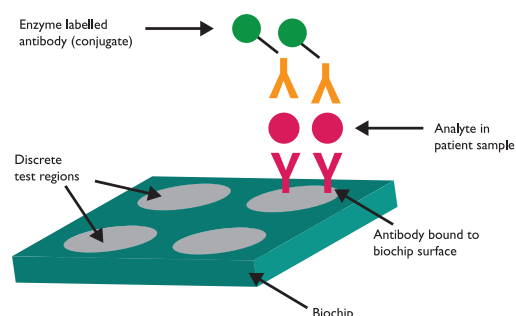
In this methodology antigens are prefabricated onto the surface of the biochip and antibodies in the sample are then bound.

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

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.

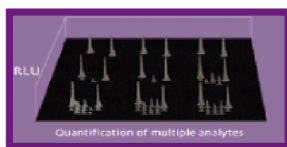
THE ART OF DETECTION - PERFECTED

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.

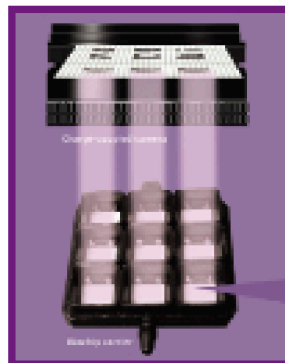
An enzyme is used to catalyse the chemical reaction on the biochip which generates the chemiluminescent signal. The light emitted from the chemiluminescent reaction that takes place in each DTR is simultaneously detected and quantified using a Charge - Coupled Device (CCD) Camera.



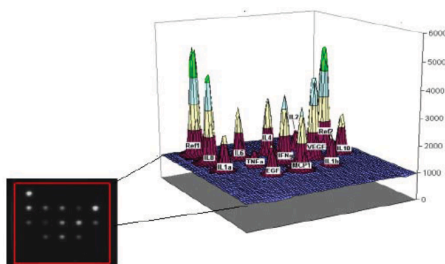
Analysis process on biochip systems



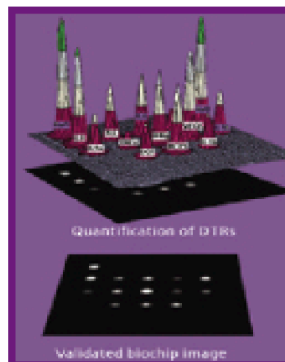
1. Unique imaging software on the analysers is used to translate the light signal into an analyte concentration.



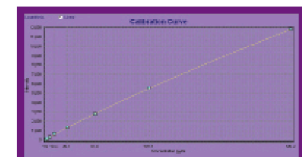
2. The CCD Camera is made up of a collection of light sensitive diodes which convert light into electrons to produce an electrical charge. The brighter the light that hits a single diode, the greater the electrical charge that will accumulate at that site.



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.

KEY FEATURES AND BENEFITS



Highly accurate testing

- BAT has a proven high standard of accurate test results CV typically <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



Small sample volume

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



Cost consolidation

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



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



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 PLATFORMS

EVIDENCE+

- Fully automated analyser
- Large sample throughput of up to 5,280 test results per hour*
- Reduced sample volume of 6-150µl
- First result is <45 minutes
- Advanced QC package
- Accurate, fast, and cost-effective solution
- Barcoded reagents and samples
- Email Alerts
- Result History

*Array dependent



MultiSTAT

- Fast, Automated & Versatile
- World's most diverse test menu facilitating on-site screening of multiple biomarkers, antimicrobials, drugs and drug metabolites
- Simple 2 step process from sample entry to results
- Results provided in as little as <30 minutes*
- CVs typically <10% with up to 98% agreement with confirmatory methods
- Cartridge based platform with kits containing all the reagents and consumables and cut-off materials

*Array dependent



EVIDENCE INVESTIGATOR

- Adaptable, efficient & comprehensive semi-automated benchtop analyser
- Throughput of 2376 tests per hour*
- World's first platform to consolidate both immunoassay and molecular diagnostics
- Reduced sample volume is required, leaving more sample remaining for confirmatory testing
- Capacity to store up to 20,000 sample results and up to 500,000 sample test results
- Seamless sample management with support for barcoded sample tubes, leveraging specially designed barcoded sheets tailored to the kit and calibrators
- Extensive QC data generation and advance retrospective reporting.

*Array dependent



DISCOVERY

- Fully automated benchtop laboratory
- Capable of molecular and immunoassay testing
- Detection of hundreds of targets from a single patient sample
- Flexible test menu in development comprising immunoassay and genetic tests for infectious diseases & oncology*
- Rapid turnaround time. 3 hours to first batch of results with results for subsequent batches every hour after**
- Simple and easy to use. Intuitive user interface guides the operator through the entire testing process
- Comprises three interconnected modules which each operate independently including nucleic acid extraction, multiplex PCR and hybridisation and detection.

*In development

**Array dependent



RANDOX - A GLOBAL DIAGNOSTIC SOLUTIONS PROVIDER

Randox has been supplying laboratories worldwide with revolutionary diagnostic solutions for over 40 years. Our experience and expertise allow us to create a leading product portfolio of high quality diagnostic tools which offer reliable and rapid diagnosis. We believe that by providing laboratories with the right tools, we can improve healthcare worldwide.

REAGENTS



Randox offers an extensive range of third-party diagnostic reagents which are internationally recognised as being of the highest quality; producing accurate and precise results. At Randox, we re-invest significantly in R&D to ensure we meet the ever-changing needs of the laboratory. Consequently, Randox offer a range of novel and superior performance assays, including: sdLDL-C, Lipoprotein (a), Copper and Zinc. Applications are available detailing instrument-specific settings for the convenient use of Randox Reagents on numerous clinical chemistry analysers.

INTERNAL QUALITY CONTROL



Acusera third party quality controls are made using the highest quality material of human origin, ensuring they react like a real patient sample. With more than 390 analytes available across the Acusera range we can uniquely reduce the number of controls required while reducing costs and time. Our product range includes clinical chemistry, immunoassay, urine, immunology and more. Qnostics molecular controls for infectious disease testing are designed to meet the demand of today's molecular diagnostics laboratory while effectively monitoring the entire testing process. Our whole pathogen molecular controls comprise hundreds of characterised viral, bacterial and fungal targets.

EXTERNAL QUALITY ASSESSMENT



RIQAS is the world's largest international EQA scheme with more than 50,000 participants worldwide. 37 comprehensive, yet flexible programmes cover a wide range of clinical diagnostic testing including chemistry, immunoassay, cardiac, urine, serology and more. Our programmes benefit from a wide range of concentrations, frequent reporting, rapid feedback and user-friendly reports. QCMD, our range of EQA programmes for molecular infectious disease testing, features a whole pathogen matrix making them a true test of patient sample analysis. With access to over 90 programmes including blood borne viruses, respiratory diseases, multi-pathogen infections and more, there is something for every laboratory.

EVIDENCE SERIES



In 2002, Randox invented the world's first, Biochip Array Technology, offering highly specific tests, coupled to the highly sensitive chemiluminescent detection, providing quantitative results instantly changing the landscape of diagnostic testing forever. The Randox Evidence Series of multi-analyte immunoanalyser's provide an unrivalled increase in patient information per sample offering diagnostic, prognostic and predictive solutions across a variety of disease areas with a highly advanced clinical and toxicology immunoassay test menu including cardiac, diabetes, drugs of abuse, metabolic, renal and stroke markers.

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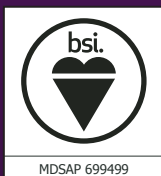


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