Molecular Diagnostics

A stratified approach to diagnostics
Introduction

Randox has 30 years experience in the development, manufacture and marketing of high quality clinical diagnostic tests and equipment. We supply over 60,000 laboratories in over 130 countries and are the sixth largest manufacturer of clinical chemistry reagents in the world. We are also the fourth largest manufacturer of quality controls and calibrators.

Research and Development is paramount within Randox as it allows us to continuously improve the standard of diagnostic materials produced. This ensures our products are the most technologically advanced in the market. Randox remains an independently owned company with its headquarters in the UK. We also have 25 international offices worldwide and distribution agreements in over 130 countries.

Randox Molecular Diagnostics (MDx) offers a range of Molecular Arrays and assay formats, providing diagnostic, prognostic and predictive solutions for a range of conditions including sexually transmitted infection, respiratory infection, coronary heart disease (CHD), familial hypercholesterolemia and colorectal cancer with many more applications currently in development. The versatility of the Randox multiplex PCR and proprietary Biochip Array Technology is exemplified by the broad range of array formats available.
Rapid multiplex SNP genotyping is based on innovative primer design which can discriminate DNA sequences which differ only at one base. Products amplified 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 position on the biochip array corresponds to a specific SNP genotype and is capable of both multiplexing and determining the zygosity of the sample.

Pathogen detection, through 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.

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.

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 three hour assay has the advantage of speed, ease of use and the ability to quickly identify multiple mutations from a single sample.
Cardiac Risk Prediction Array
Simultaneous genotyping of 19 SNPs for a reliable CHD risk assessment

Introduction
Coronary Heart Disease (CHD) is the leading cause of death in the developed world and its prevention is a core activity in general practice worldwide. For example, clinical guidelines from the Joint Cardiac Societies and NICE in the UK recommend that patients at greater than 20% risk of CHD in the next ten years should be classified as high risk and considered for intensive lifestyle intervention and lipid lowering therapy, primarily the prescription of statins.

Current CHD risk assessment tools based on common risk factors such as blood pressure and blood cholesterol levels (eg. PROCAM and Framingham) have low predictive value and take no account of genetic predisposition to CHD. Cooper et al reported only 14% of CHD events during a ten year period were predicted by these algorithmic tools.

In recent years Genome Wide Association Studies (GWAS) have been carried out to identify genetic variants associated with CHD. This involves comparing millions of loci in the genomes of a population suffering from CHD and a control population. Meta-analysis of such studies has identified 18 variants (referred to as single nucleotide polymorphisms (SNPs)) as being associated with CHD. Individually, the presence of an “at risk” variant does not greatly increase the risk of developing CHD. However, the presence of multiple “at risk” alleles can increase the risk of developing CHD two-fold or greater, an effect similar to being a current smoker. Combining such genotype information with common risk factors could allow individuals to be more accurately classified and preventative therapies and lifestyle advice targeted to those who require it most.

The Cardiac Risk Prediction Array
In order to utilise the GWAS findings in a clinical setting, individuals require to be genotyped for each of the 18 CHD “at risk” SNPs. At present this can be a time consuming and expensive process. Together with key opinion leaders in cardiovascular genetics, Randox has developed a rapid array which will allow all 18 SNPs to be genotyped simultaneously. Firstly, a multiplex PCR reaction is performed, where the products amplified correspond to the genotype of the patient sample. The PCR products are then hybridised onto the CHD risk biochip array and imaged using the Evidence Investigator analyser to identify which PCR products are present. Thus a patient sample can be genotyped within one day. The genotype information is then put into an algorithm which weights each SNP and calculates a CHD genetic risk score. The CHD genetic risk score is combined with common risk factors and an overall CHD risk score is calculated.

CHD Risk Prediction

<table>
<thead>
<tr>
<th>SNP</th>
<th>Presence of risk allele</th>
<th>Algorithm</th>
<th>Genetic Risk Score</th>
<th>CHD Risk</th>
<th>Lifestyle Choices</th>
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<tbody>
<tr>
<td>SNP 1</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>SNP 2</td>
<td>-</td>
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<tr>
<td>SNP 3</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>etc</td>
<td></td>
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</tr>
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</table>

Common Risk Factors
eg. Blood Pressure
Blood Cholesterol

Framingham Score
PROCAM etc
Response to statin treatment

A further important SNP which can predict response to particular statin therapies has been included in the array. Individuals who are homozygous (frequency =0.13) for the risk allele are 17 times more likely to suffer from statin-induced myopathy when treated with high doses of simvastatin.\(^8\) Identifying patients with a higher risk of suffering statin-induced myopathy would allow clinicians to make more informed decisions when prescribing lipid lowering therapies.

Cardiac Risk Prediction Array Protocol

Benefits of the Cardiac Risk Prediction Array

**To the patient**
- Randox Cardiac Risk Prediction Array is a rapid simple method for reliable genetic risk assessment of CHD
- Combined with common risk factors, the array allows more accurate classification and preventative actions to be taken
- Identifies patients genetically predisposed to statin-induced myopathy

**To the laboratory**
- Simple and rapid protocol allows a patient sample to be genotyped in one day
- Streamlined workflow – protocol and reagents optimised for the molecular laboratory
- 36 patient samples can be processed per kit
- Easy to interpret results using Randox Evidence Investigator dedicated software
- All 19 SNPs can be genotyped simultaneously
Familial Hypercholesterolemia (FH) is a genetic disorder of lipoprotein metabolism. It is characterised by high levels of low density lipoprotein (LDL) and early onset of cardiovascular disease. Three main genes which are known to cause FH are low density lipoprotein receptor gene (LDLR), apolipoprotein B (ApoB) and proprotein convertase subtilisin/kexin-type 9 (PCSK9).

Many patients have mutations in the LDLR gene that encodes the LDL receptor protein, which normally removes LDL from the circulation, or in ApoB, which is the part of LDL that binds with the receptor. PCSK9 encodes an enzyme that is involved in regulating the degradation of the LDL receptor protein.

Patients who have one abnormal copy (heterozygous) of these genes may have premature cardiovascular disease between the ages of 30 and 40. Having two abnormal copies (homozygous) may cause severe cardiovascular disease in childhood. Heterozygous FH is a common genetic disorder, occurring in 1 in 500 people in most countries; whereas homozygous FH is much rarer, occurring in 1 in a million births. Heterozygous FH, when detected early can be successfully treated with statins, bile acid sequestrants or other hyalopipidemic agents that lower cholesterol levels. Accurate diagnosis can therefore lead to more tailored treatments and better patient outcomes.

The most common genetic defects in FH are LDLR mutations (prevalence of 1 in 500, depending on the population), ApoB mutations (prevalence of 1 in 1000) and PCSK9 mutations (prevalence less than 1 in 2500). The FH biochip array detects 19 mutations known to influence the function of these three genes, with the majority from the LDLR gene. This panel of mutations can detect 60% of FH positive patients.

Familial Hypercholesterolemia (FH) Array
Rapid simultaneous detection of mutations within the LDLR, ApoB and PCSK9 genes

Introduction
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Principle of the Familial Hypercholesterolemia Array

The FH array is based on a combination of multiplex PCR and biochip array hybridisation. Innovative PCR priming technology permits high discrimination between multiple wildtype and mutant DNA regions in a number of genes. A unique primer set is designed for each mutation target (and control), which will hybridise to a complementary discrete test region (DTR) on the Randox proprietary biochip array. This combination of Randox priming and spatially organised biochip array technology enables high multiplexing of the assay. Analysis can be completed from template DNA through PCR to data readout in 3 hours.
Intended use

The FH Array is intended for the simultaneous qualitative detection of mutations in 19 targets within the low density lipoprotein receptor gene (LDLR), apolipoprotein B (ApoB) gene and proprotein convertase subtilisin/kexin-type 9 (PCSK9) gene. The sample type is genomic DNA extracted from blood.

Clinical data

Several validation studies were completed using FH samples, with both blinded and unblinded samples assessed. Total correlation of 98% was observed when using the FH array.

FH Array Protocol

**Save time and cost**
with simultaneous mutation detection using the FH Array

**Step 1**
Extraction
Genomic DNA extracted from blood

**Step 2**
Amplification
Multiplex PCR reaction

**Step 3**
Hybridisation
Amplicon hybridisation/conjugation to biochip array

**Step 4**
Detection
Imaging and result processing by Evidence Investigator

The FH Array detects 19 mutations in the three genes LDLR, ApoB and PCSK9

Benefits of the Familial Hypercholesterolemia Array

- The FH array is a rapid simple method for determining mutational status
- Samples can be assessed in small batches (as low as 3 samples)
- Easy to interpret results using the Evidence Investigator dedicated software
- Turnaround time of ~3 hours
- Streamlined workflow - protocol and reagents optimised for the molecular laboratory
- System can be used to detect single base changes, insertions and deletions, within the same multiplex PCR
- Only 20ng of genomic DNA required

**in the UK and Ireland**
KRAS, BRAF, PIK3CA* Array
Rapid profiling of point mutations in the KRAS, BRAF and PIK3CA genes

Introduction
Colorectal cancer (CRC) is the third most common cancer worldwide.\(^1\) Metastatic disease accounts for 40-50\% of newly diagnosed patients and is associated with high morbidity.\(^1\)\(^3\)\(^4\) Despite recent therapeutic advances, the prognosis for patients with metastatic CRC (mCRC) remains poor.\(^1\)\(^3\)\(^4\) In recent years monoclonal antibodies (moAbs), like cetuximab and panitumumab which target the epidermal growth factor receptor (EGFR), have proven to be effective in combination with chemotherapy or as single agents for the treatment of mCRC.\(^1\)\(^5\)\(^6\) These moAbs block the signal from EGFR inhibiting downstream signalling including KRAS, BRAF and PIK3CA mediated events (see diagram below). However, when KRAS, BRAF and PIK3CA are mutated they are permanently ‘turned on’ permitting downstream events irrespective of anti-EGFR therapy. The Randox KRAS, BRAF, PIK3CA Array allows the clinician to detect important mutations in the KRAS, BRAF (and PIK3CA) genes, enabling the appropriate selection of patients for therapy.

EGFR pathway and its inhibition by EGFR targeted monoclonal antibodies

Targets detectable by the KRAS, BRAF, PIK3CA Array
The KRAS, BRAF, PIK3CA Array is designed for the rapid qualitative detection of point mutations within the genes KRAS, BRAF and PIK3CA from fresh/frozen and formalin fixed paraffin embedded tissue DNA (refer to below table for targets detectable).

<table>
<thead>
<tr>
<th>KRAS</th>
<th>BRAF</th>
<th>PIK3CA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>codon 12</strong></td>
<td><strong>codon 13</strong></td>
<td><strong>codon 61</strong></td>
</tr>
<tr>
<td>G12A</td>
<td>G12C</td>
<td>G13D</td>
</tr>
<tr>
<td>G12R</td>
<td>G12S</td>
<td>G13C</td>
</tr>
<tr>
<td>G12D</td>
<td>G12V</td>
<td>G13R</td>
</tr>
</tbody>
</table>

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[^1]: Reference number
[^2]: Reference number
[^3]: Reference number
[^4]: Reference number
[^5]: Reference number
[^6]: Reference number
Why test the KRAS, BRAF, and PIK3CA genes?

Early studies conducted on mainly heavily pre-treated chemotherapy-refractory patients and also chemotherapy-naive patients with mCRC indicated that only 10-20% of patients clinically benefited from anti-EGFR moAbs. Consequently oncogetic activation of EGFR downstream effectors was investigated with respect to clinical outcome to moAb therapy. Analysis confirmed that patients with mCRC carrying activating KRAS gene mutations do not benefit from anti-EGFR moAb therapy. KRAS mutations have since emerged as the major negative predictor of efficacy in patients receiving cetuximab or panitumumab. The occurrence of KRAS mutations however only accounts for approximately 35-45% of nonresponsive patients. The identification of additional genetic determinants of primary resistance to EGFR-targeted therapies in colorectal cancers is therefore important. Recent studies have focused on the molecular analysis of the molecules involved in downstream EGFR signalling with mutations in the BRAF and PIK3CA genes being reported to affect patient response to EGFR-targeted moAbs.

**Additional Array Applications**

Mutations on this array are also implicated in other cancers such as KRAS in lung cancer and PIK3CA in breast cancer.

**KRAS, BRAF, PIK3CA Array Protocol**

**Step 1: Extraction**
Genomic DNA is extracted from fresh/frozen or FFPE tissue samples.

**Step 2: Amplification**
Single tube multiplex PCR reaction.

**Step 3: Hybridisation**
Amplion hybridisation/conjugation to biochip array.

**Step 4: Detection**
Imaging and result processing by Evidence Investigator.

**Multiple Mutation Profiling**
The KRAS, BRAF, PIK3CA Array detects 20 mutations in these three genes, which are implicated in mCRC therapy response using the revolutionary biochip array technology.

**Benefits of the KRAS, BRAF, PIK3CA Array**

- Streamlined workflow – protocol and reagents are optimised for the molecular laboratory
- Compatible with a broad range of genomic DNA input and type:
  - Formalin fixed paraffin embedded (FPPE) tissue
  - Fresh/frozen tissue
- Detection of 1% mutant in a background of wildtype genomic DNA
- Single DNA sample required
- Single reaction multiplex PCR coupled to a biochip provides greater mutation coverage of the three most important genes (KRAS, BRAF and PIK3CA) implicated in metastatic colorectal cancer therapy response
- Turnaround time of three hours
Respiratory Pathogen Array
Rapid, simultaneous detection of 22 bacterial and viral respiratory pathogens

Introduction
The Randox Respiratory Pathogen Array is a multiplex array intended for the simultaneous detection of 22 respiratory pathogens in individuals suspected of Respiratory Tract Infections (RTIs). The ability to simultaneously detect up to 15 respiratory viruses and 7 bacterial respiratory pathogens in one sample provides clinicians with a comprehensive patient profile, enabling faster and more appropriate treatment decisions when they matter most. The Respiratory Pathogen Array is based on a combination of multiplex PCR, probe hybridisation and chemiluminescence detection using the Evidence Investigator analyser. This user friendly array can run 54 samples simultaneously in five hours.

Respiratory Pathogen Array detects the following 22 bacterial and viral pathogens

- Moraxella catarrhalis
- Streptococcus pneumoniae
- Staphylococcus aureus
- Haemophilus influenza
- Legionella pneumophila
- Chlamydophila pneumoniae
- Mycoplasma pneumoniae
- Human respiratory syncytial virus A
- Influenza A
- Influenza B
- Human respiratory syncytial virus B
- Human parainfluenza virus 1
- Human parainfluenza virus 2
- Human parainfluenza virus 3
- Human parainfluenza virus 4
- Human coronavirus 229E/NL63
- Human coronavirus OC43/HKU1
- Human adenovirus A/B/C/D/E
- Human rhinovirus A/B
- Human metapneumovirus
- Human bocavirus 1/2/3
- Human enterovirus A/B/C
- Streptococcus pneumoniae
- Haemophilus influenza
- Staphylococcus aureus
- Mycoplasma pneumoniae
- Human respiratory syncytial virus A
- Influenza A
- Influenza B
- Human respiratory syncytial virus B
- Human parainfluenza virus 1
- Human parainfluenza virus 2
- Human parainfluenza virus 3
- Human parainfluenza virus 4
- Human coronavirus 229E/NL63
- Human coronavirus OC43/HKU1
- Human adenovirus A/B/C/D/E
- Human rhinovirus A/B
- Human metapneumovirus
- Human bocavirus 1/2/3
- Human enterovirus A/B/C

Clinical significance
Respiratory diseases are increasingly common and are a leading cause of hospitalisation and death, particularly in immunocompromised patients and the elderly. Respiratory tract infections affect the air passages, including the nasal passages, the bronchi and the lungs. These infections can manifest themselves through a range of conditions including bronchitis, pneumonia, through to asthma and chronic obstructive pulmonary disease (COPD). Admissions to hospital due to respiratory diseases are high, taking up much needed beds. Early detection and diagnosis would dramatically reduce hospitalisation rates and length of stay, thus reducing associated costs and time.
The ability to simultaneously identify the most prevalent pathogens, both viral and bacterial, will provide a rapid and more cost-effective diagnostic tool than current tests that only look for single pathogens. This greatly benefits the patient as it reduces the time from presentation to treatment and minimises sample requirements. It also benefits healthcare systems as correct and timely treatment will reduce bed stays and may improve antibiotic usage. The Randox Respiratory Pathogen Array offers these advantages providing clinicians with a more complete infection profile.

Why use the Respiratory Pathogen Array?

The ability to simultaneously identify the most prevalent pathogens, both viral and bacterial, will provide a rapid and more cost-effective diagnostic tool than current tests that only look for single pathogens. This greatly benefits the patient as it reduces the time from presentation to treatment and minimises sample requirements. It also benefits healthcare systems as correct and timely treatment will reduce bed stays and may improve antibiotic usage. The Randox Respiratory Pathogen Array offers these advantages providing clinicians with a more complete infection profile.

Respiratory Pathogen Array Protocol

**Step 1**
Extraction
RNA and DNA is extracted from bronchoalveolar lavage, nasopharyngeal swab, sputum or saliva samples

**Step 2**
Amplification
Single tube multiplex RT/PCR reaction

**Step 3**
Hybridisation
Amplicon hybridisation to biochip array – each biochip can detect 22 pathogens

**Step 4**
Detection
Imaging and results processing by Evidence Investigator

Benefits of the Respiratory Pathogen Array

- Semi-quantitative testing – allowing determination of primary infection
- Comprehensive profile of pathogens identifies secondary or multiple infections which may otherwise remain untreated
- Rapid turnaround time of five hours
- May prevent the spread of infection through early and more appropriate intervention
- May reduce antibiotic misuse
- Reduced sample requirement – of particular relevance to young and infirm patients
- Compatible with various sample matrices
- Increased specificity through biochip hybridisation
- Spatial separation on biochips allows clear diagnosis
Sexually Transmitted Infection Array  
Rapid, simultaneous detection of 10 STIs

Introduction
The Randox Sexually Transmitted Infection (STI) Array far exceeds current STI tests on the market. The assay is based on a combination of multiplex PCR, probe hybridisation and chemiluminescence detection to allow screening of viral and bacterial STIs. The multiplex array rapidly screens for the presence of 10 different STIs simultaneously from one patient sample. The simultaneous detection of these infections provides a comprehensive profile for each patient. This will enable the clinician to decide on the best treatment options decreasing antibiotic misuse and the risk of the infection spreading. The STI array is optimised for use on the Evidence Investigator Analyser, which utilises the revolutionary Biochip Array Technology.

The Randox STI Array detects 10 STIs in one sample

Clinical significance
STIs and related complications represent a significant public health issue in both developed and developing countries. Many infections are asymptomatic and remain undiagnosed, increasing the risk of unhindered spread. STIs may induce serious complications that reduce fertility, increase risk of ectopic pregnancies and increase infant mortality. Existing technologies or screening programmes do not meet the social or clinical need. Randox has developed this multiplex PCR assay coupled to Biochip Array Technology to provide a rapid, efficient and reliable clinical solution to STI detection. Simultaneous screening for multiple STIs will identify specific viral, protozoan or bacterial pathogens, permitting targeted antibiotic/anti-viral therapy. This will also identify secondary infections, which may otherwise remain undiagnosed.
The World Health Organisation quote 448 million new infections of curable sexually transmitted infections (syphilis, gonorrhoea, chlamydia and trichomoniasis) occur annually therefore early and accurate detection is critical.²³

### STI Array Protocol

#### Step 1
Extraction
Genomic DNA is extracted from urine or urogenital swab samples

#### Step 2
Amplification
Single tube multiplex PCR reaction

#### Step 3
Hybridisation
Amplicon hybridisation/conjugation to biochip array - each biochip can detect 10 STIs

#### Step 4
Detection
Imaging and result processing by Evidence Investigator

### Benefits of the STI Array

- Simultaneously detect up to 10 STIs from a single patient sample
- Save time and cost associated with single infection detection
- Reduced sample requirements
- Detection of asymptomatic co-infections
- Added specificity due to combination of stringent PCR and array hybridisation
- Rapid turnaround time from sample to result in less than five hours
- Clear and easy results interpretation
- Internal controls for the three critical assay steps
- Ability to test DNA from multiple sample matrices
- Use existing automated extraction methodology
- 54 patient samples can be processed simultaneously, with multiple runs possible in one working day
The Evidence Investigator is a semi-automated, benchtop biochip analyser which offers complete patient profiling.

*Save time and costs* -
Multiplexing reduces time, labour and reagents associated with multiple individual tests

*Increase throughput* -
For greater laboratory efficiency

*Consolidation* -
Of immunoassays and molecular diagnostics, improving laboratory efficiency

*Result traceability* -
Chain of custody features and bar coded reagents

*No hidden costs* -
Package includes imaging module, PC and imaging software, thermostraker, biochip carrier handling tray and barcode scanner

*Ease of operation* -
Straightforward testing procedure, ready-to-use biochips and minimal sample handling

*Extensive QC* -
Internal quality controls ensure all key assay steps have been performed correctly i.e. extraction and amplification

*Retrospective reporting* -
Enabling additional analysis of previously captured sample data

### Ordering Details

<table>
<thead>
<tr>
<th>Description</th>
<th>Size</th>
<th>Cat. No.</th>
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<tbody>
<tr>
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<td>EV3836A &amp; EV3836B</td>
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<tr>
<td>Familial Hypercholesterolemia Array</td>
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<td>Sexually Transmitted Infection Array</td>
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*Note: Extraction reagents are not included*

### Also In Development

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<thead>
<tr>
<th>Description</th>
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<tr>
<td>Breast Cancer Expression Array</td>
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<tr>
<td>Pharmacogenomic Arrays</td>
<td>including CYP2D6, Anti-coagulant Array</td>
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</table>
Cardiac Risk Prediction Array


Familial Hypercholesterolemia Array


KRAS, BRAF, PIK3CA Array


Sexually Transmitted Infection Array

23. World Health Organisation, Fact sheets №110, August 2011 www.who.int/mediacentre/factsheets/fs110