stratec

# The InviGenius® PLUS

## Walk-away DNA/RNA sample preparation

# CONTENT

## THE INVIGENIUS® PLUS


Superior automated sample preparation ..... 2

InviGenius® PLUS deck layout ..... 3

Ultimate safety of set-up and operation ..... 4

Fully automated, walk-away DNA/ RNA purification ..... 6

Nucleic acid extraction principle ..... 8


## KITS AND APPLICATIONS


Kits and applications ..... 9

1. Automation for oncology ..... 10

2. One kit for DNA/RNA isolation from pathogens ..... 12

3. Genetic testing from 2 ml of blood ..... 14


## SPECIFICATIONS AND ORDERING INFORMATION


Specifications ..... 15

Ordering Information ..... 16

# SUPERIOR AUTOMATED SAMPLE PREPARATION

Magnetic separation module for binding of magnetic particles

Simple operation via touchscreen for protocol selection and system set up

Built-in PC with unidirectional LIMS connectivity

Sample and reagent loading racks for barcoded labware with integrated barcode reader

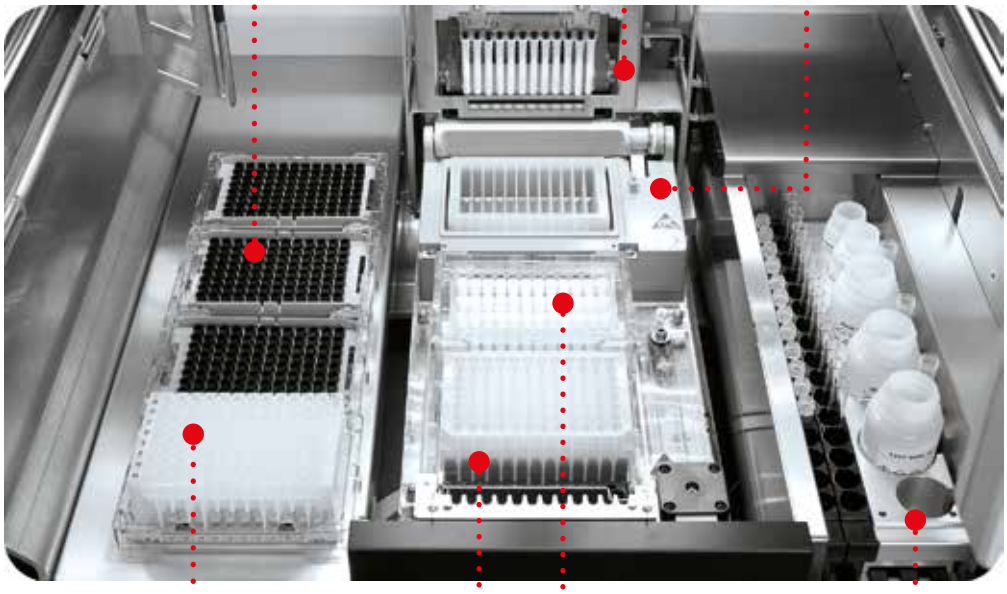
Waste station

The InviGenius® PLUS is a walk-away system for nucleic acid purification for up to 12 samples from up to 4 ml of sample volume. Innovative functionality and optimized protocols for demanding samples and applications result in reliable performance and superior DNA and RNA quality for molecular diagnostics*.

The combination of well-established magnetic bead based InviMag® technology and state-of-the-art process automation allows for standardization and streamlining of laboratory workflows.

*) In compliance with the Directive 98/79/EC on in vitro diagnostic medical devices (IVD-Directive). Products which are CE-marked according to the IVD-Directive can be used for diagnostic applications in countries where this directive is recognized. The device is not approved by the US FDA.

# INVIGENIUS® PLUS DECK LAYOUT




## THE NEW PLUS FEATURES

1. Deep-well working plate for sample volumes of up to 4 ml
2. Heat lysis and heat elution for high recovery rates of nucleic acids from demanding samples such as liquid biopsies or virus samples
3. Barcoded labware for complete sample traceability (e.g. 2 ml barcoded elution tubes)
4. Choice of elution tubes or plates for flexible sample management
5. Droplet catcher minimizes the risk of cross contamination

# ULTIMATE SAFETY OF SET-UP AND OPERATION

The InviGenius® PLUS delivers exceptional process safety in a completely monitored operation environment. Elaborate software control and intuitive user guidance enable full process control and documentation and prevent sample tracking errors.

## 1. LOADING RACKS FOR PRIMARY TUBES

Integrated barcode reader for sample identification during loading

- Prevention of human errors
- Tracking of samples
- Connectivity with LIMS allowing workflow continuity and archiving of the data

Examples of compatible primary tubes:

- Sarstedt Monovette®
- BD Vacutainer®
- TERUMO Venosafe®
- Greiner Bio-One Vacuette®

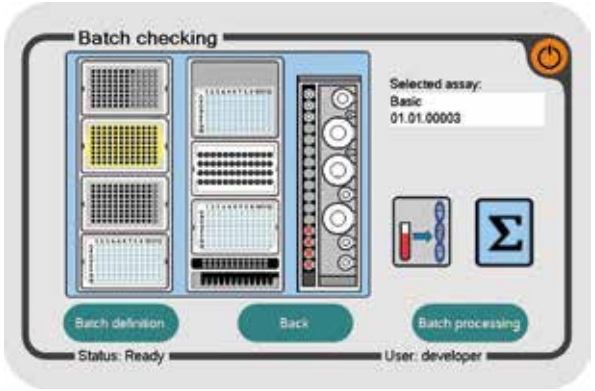
## 2. LOADING RACK WITH FLEXIBLE REAGENT POSITIONING

Automated reagent detection – independent of position

- Prevention of human errors
- Verification of correct reagents
- Verification of valid expiration dates

## 3. PLUG-IN FOR SEPARATE HAND-HELD BARCODE SCANNER

- Choice of elution tubes or plates
- Complete traceability for all plastic ware




## 4. SOFTWARE-SUPPORTED SETUP OF REAGENTS, WASTE AND DISPOSABLES

- Inventory checks before and during run
- Defined and protected protocols prevent user-errors

## 5. AIR DISPLACEMENT PIPETTOR

- Barometric and conductive liquid level detection
- Reduced maintenance and waste - no system liquid is required
- Prevention of cross contamination through use of filter tips and intelligent routing

### Additional pipetting options

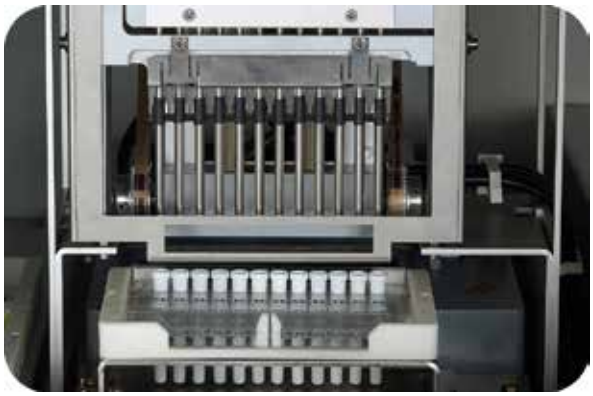
- Aliquot pipetting of eluates for generation of replicates, e.g. for PCR
- Pre-mix of samples to prevent clogging and for sample resuspension

# FULLY AUTOMATED, WALK-AWAY DNA/ RNA PURIFICATION

The InviGenius® PLUS is a true walk-away system for DNA/RNA extraction and purification from clinical samples – providing a reliable "Sample in – Eluate out" technology!

## 1. HEAT INCUBATOR

- Automated heat lysis (up to 95 °C) on board
- A heated lid prevents aerosol formation and condensation
- Suitable for deep-well working plate for sample volumes of up to 4 ml



## 2. MAGNETIC SEPARATION MODULE

- Twelve magnetic rods transfer magnetic beads and mix samples
- Disposable sheath racks for several runs
- Bottom magnets prevent carry-over of beads into the eluate
- Droplet catcher prevents cross-contamination

## 3. WASTE MANAGEMENT AND DECONTAMINATION

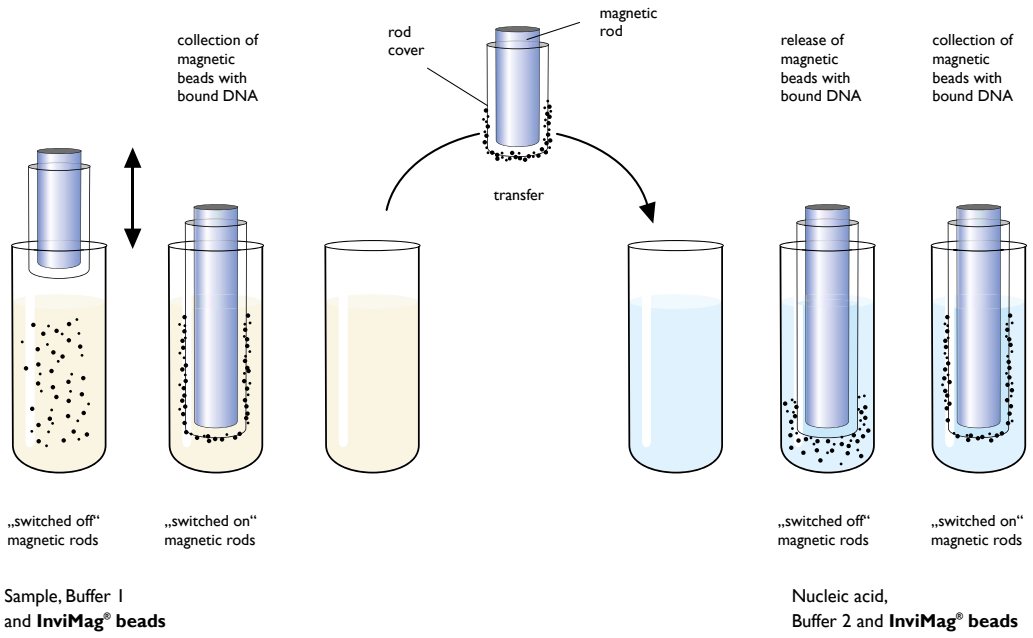
- Used tips and sheaths will be disposed into the waste container; Pipettor drips excessive liquid into it
- Waste container is rotating slowly for better utilization and can be removed and disposed
- UV light enables decontamination of the worktable

### Advanced troubleshooting

- Acoustic signal, e.g. in case of closed bottles, clotted sample
- Flagging of problematic samples, e.g. clots
- Automatic hard disk space management

# NUCLEIC ACID EXTRACTION PRINCIPLE

The InviGenius® PLUS controls an array of magnetic rods that can collect or release magnetic particles. After sample lysis the nucleic acids are bound to the magnetic particles and transferred through the extraction, purification, and elution processes. This circumvents pipetting errors. The eluted pure nucleic acids are ready-to-use for subsequent downstream applications.




The InviMag® technology for the InviGenius® PLUS system increases laboratory efficiency by minimizing the need for individual kits for different applications for a broad range of starting materials. Sample volumes up to 4 ml can be processed, providing superior sensitivity for genomic applications and pathogen detection.

## STARTING MATERIALS

Whole blood, FFPE samples, serum, plasma, urine, stool*, sputum*, BAL, swab, saliva, transport media

*) Sample pretreatment is necessary

## TARGET NUCLEIC ACIDS

Genomic DNA, cell-free circulating DNA, RNA & DNA from viruses, bacterial DNA

# KITS AND APPLICATIONS


| Nucleid Acid | Starting Material | Product Name |
|---|---|---|
| Genomic, bacterial, viral DNA & viral RNA | 200 µl whole human blood (EDTA, citrate), plasma, serum, cell-free body fluids, rinse liquid from swabs, supernatant from stool suspensions, sputum, BAL, urine | InviMag® Universal Kit/ IG |
| Genomic DNA | 200 µl whole human blood (EDTA, citrate)<br>2 ml whole human blood (EDTA, citrate) | InviMag® Blood DNA Mini Kit/ IG<br>InviMag® Blood DNA Maxi Kit/ IG |
| | 1.6 ml SalivaGene® stabilized saliva samples | InviMag® SalivaGene DNA Kit/ IG |
| | FFPE tissue, fresh biopsy samples, cryosections | InviMag® FFPE DNA Kit/ IG |
| Cell-free DNA | up to 4 ml plasma, serum, urine | InviMag® Free Circulating DNA Kit/ IG |
| Bisulfite converted DNA | 500 pg to 5 µg genomic DNA | InviMag® Bisulfite Conversion Kit/ IG |

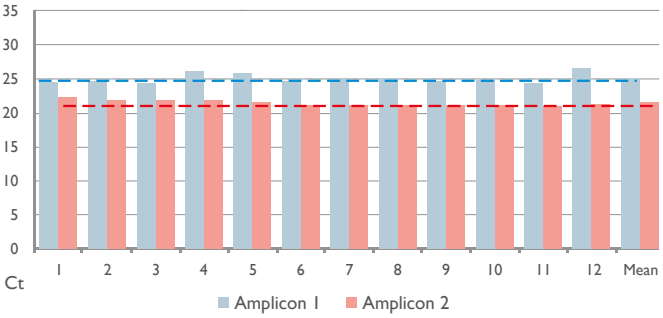
The InviMag® technology incorporates many years of experience in developing magnetic bead based kits for automated systems. The InviMag® kits rely upon STRATEC Molecular proprietary formulations and ensure superior results for the extraction and purification of DNA and RNA.

# 1. AUTOMATION FOR ONCOLOGY

## a) EXTRACTION OF CELL-FREE CIRCULATING DNA

The InviMag® Free Circulating DNA Kit/ IG enables efficient, fully automated purification of cell-free circulating DNA (cfDNA) fragments from 4 ml of plasma or serum samples on the InviGenius® PLUS.

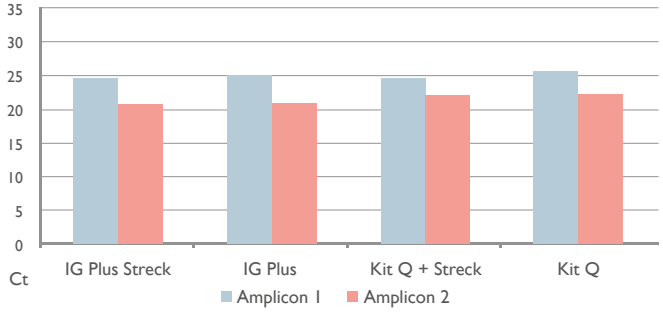
### Fig. 1: Excellent and reproducible intra-run recovery of circulating cfDNA




*Circulating cell-free DNA was isolated from 12 aliquotes of 4 ml Seracon plasma samples in parallel using the InviMag® Free Circulating DNA Kit/ IG on the InviGenius® PLUS and eluted in 100 µl. DNA yield was quantified by real-time PCR of two amplicons within the 18S rRNA sequence.*

- FAM (70 bp) CT Std. Dev: 0.72
- Cy5 (177 bp) CT Std. Dev: 0.33

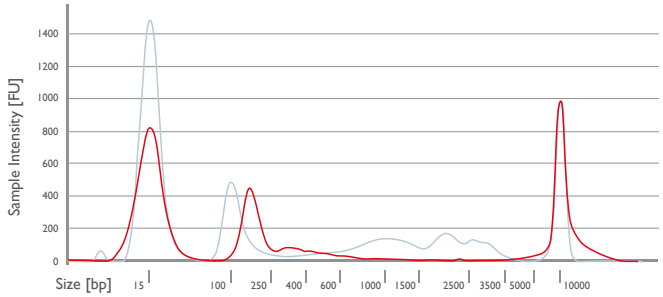
### Fig. 2: Comparison of extraction efficiency using automated and manual kits




*cfDNA was isolated from 4 ml plasma (same blood collected in Streck tubes and EDTA tubes) using the fully automated procedure of the InviMag® Free Circulating DNA Kit/ IG on the InviGenius® PLUS in comparison to a manual kit. DNA was quantified by real-time PCR of two amplicons within the 18S rRNA sequence (70 bp & 177 bp). Samples collected with Streck tubes yield comparable results to conventional EDTA tubes and the extraction efficiency is at least comparable to competition.*

- FAM (70 bp) CT Std. Dev: 0.72
- Cy5 (177 bp) CT Std. Dev: 0.33

### Fig. 3 Case study with 68 plasma samples - Fragment analysis on TapeStation




*TapeStation 4200 electropherogram of InviMag® extracted cfDNA (red) compared with Q extracted cfDNA (blue) from 8 ml of plasma samples. Fragment analysis by TapeStation showed the characteristic cfDNA fragments of 170 bases in most of the extractions from both methods. Nevertheless some Q extractions showed additional signals of fragments above 500 bases.*

*Data kindly provided by Professor Jacqui Shaw and Dr Caroline Cowley, Leicester Cancer Research Centre, University of Leicester, UK*

## Fig. 4: Sequencing metrics show higher read depth for the InviMag® method in 3 of 4 samples

| Sample Name | Gene ID | Allele Name | Variant | Total Read Coverage | Allele Read Coverage | Allele Read Frequency | Total Molecular Coverage | Allele Molecular Coverage | Allele Molecular Frequency |
|---|---|---|---|---|---|---|---|---|---|
| Competitor Q - A | TP53 | p.M237I | T | 210696 | 0 | 0 | 4283 | 0 | 0 |
| InviMag® - A | TP53 | p.M237I | T | 192580 | 45 | 0.02 | 4154 | 3 | 0.07 |
| Competitor Q - A | TP53 | p.Y200C | C | 94033 | 167 | 0.18 | 3052 | 5 | 0.16 |
| InviMag® - A | TP53 | p.Y200C | C | 81237 | 101 | 0.12 | 2286 | 2 | 0.09 |
| Competitor Q - B | TP53 | p.R273C | A | 76423 | 27 | 0.04 | 3706 | 2 | 0.05 |
| InviMag® - B | TP53 | p.R273C | A | 116962 | 54 | 0.05 | 7388 | 4 | 0.05 |
| Competitor Q - C | EGFR | p.E746_A750delELREA | - | 159796 | 28013 | 17.53 | 2389 | 657 | 27.50 |
| InviMag® - C | EGFR | p.E746_A750delELREA | - | 122372 | 25809 | 21.09 | 6213 | 2025 | 32.59 |
| Competitor Q - C | EGFR | p.T790M | T | 76409 | 4359 | 5.71 | 1080 | 66 | 6.11 |
| InviMag® - C | EGFR | p.T790M | T | 120911 | 6261 | 5.18 | 5020 | 275 | 5.48 |
| Competitor Q - C | TP53 | p.R158L | A | 36373 | 0 | 0 | 323 | 0 | 0 |
| InviMag® - C | TP53 | p.R158L | A | 103963 | 115 | 0.11 | 2913 | 5 | 0.17 |
| Competitor Q - D | BRAF | p.V600E | T | 62493 | 43 | 0.07 | 1211 | 2 | 0.17 |
| InviMag® - D | BRAF | p.V600E | T | 15076 | 0 | 0.00 | 541 | 0 | 0 |
| Competitor Q - D | TP53 | p.R248W | A | 97158 | 456 | 0.47 | 2065 | 7 | 0.34 |
| InviMag® - D | TP53 | p.R248W | A | 180266 | 1417 | 0.79 | 7333 | 55 | 0.75 |

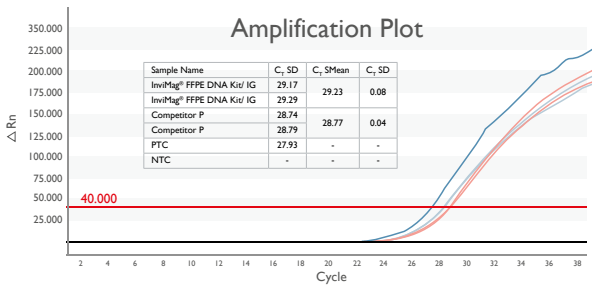
*Plasma samples from different cancer patients (Breast Cancer, Non-Small Cell Lung Cancer, Small Cell Lung Cancer, Metastatic Melanoma) were used as starting material. cfDNA was isolated from 4 ml of plasma into an elution volume of 80 µl using the InviMag® Free Circulating DNA Kit/ IG on the InviGenius® PLUS in comparison to a manual kit Q. Targeted Next Generation Sequencing (Oncomine cfDNA assay, Thermofisher) showed comparable results (VAF) with both extraction methods.*

*Data kindly provided by Professor Jacqui Shaw and Dr Caroline Cowley, Leicester Cancer Research Centre, University of Leicester, UK*

## b) FULLY AUTOMATED DNA EXTRACTION FROM FFPE SLIDES

The InviMag® FFPE DNA Kit/ IG enables efficient, fully automated purification of genomic DNA fragments from FFPE slides on the InviGenius® PLUS. No manual pretreatment like deparaffination or formalin removal is required. The automated procedure reduces the pure hands-on time from 60 min to 10 min.

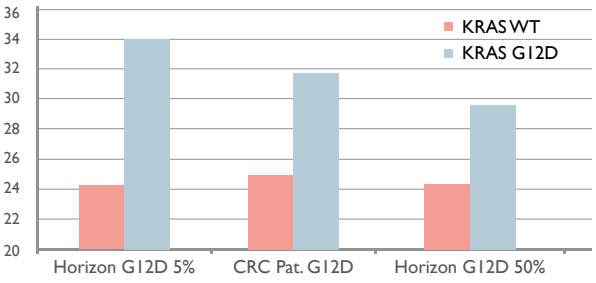
### Fig. 5 Comparable results using different manual and automated isolation methods




*DNA was isolated from one FFPE slide of a primary tumor (duplet) using a manual kit from competitor P (blue curves) and fully automated using the InviMag® FFPE DNA Kit /IG on the InviGenius® PLUS (pink curves). The extracted DNA was analyzed in a K-ras specific real-time PCR. The amplification plot shows comparable CT values for both extraction methods (measured in duplicates).*

*Pink: InviMag® FFPE DNA Kit /IG (prototype)*
*Green: Positive control*
*Blue: Competitor P*

### Fig.6 KRAS mutation detection in a patient sample



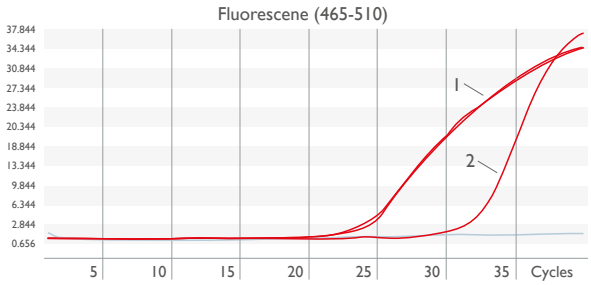

*DNA extracted fully automated from FFPE sections using the InviMag® FFPE DNA Kit /IG on InviGenius® PLUS were subjected to the InviGene® KRAS 12/13 Kit defined FFPE sections (Horizon Discovery) with an allelic frequency of 5 and 50% KRAS G12D.*

*a) defined FFPE sections (Horizon Discovery) with an allelic frequency of 5 % KRAS G12D*
*b) FFPE section with a KRAS G12D mutation (confirmed by Sanger sequencing) from a colorectal cancer (CRC) patient, lying between 50% and 5% due to the detectable mutation rates from 5 - 50% by Sanger Sequencing*
*c) defined FFPE sections (Horizon Discovery) with an allelic frequency of 50 % KRAS G12D*

# 2. ONE KIT FOR DNA/RNA ISOLATION FROM PATHOGENS

The InviMag® Universal Kit/ IG enables fully automated purification of genomic, bacterial, viral DNA and viral RNA from a variety of clinical samples on the InviGenius® PLUS with sample volumes of up to 200 µl. Different primary tubes can be placed directly into the sample loading rack.

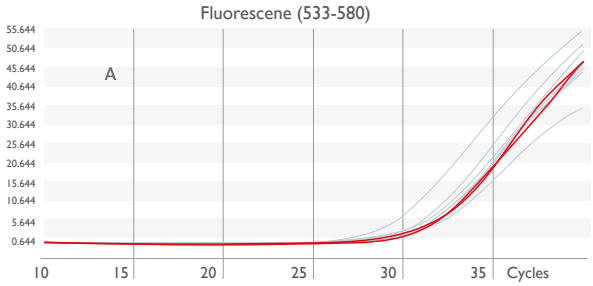
## Fig. 1: Viral RNA from sputum




*RNA from human metapneumovirus was isolated from sputum samples using the InviMag® Universal Kit/ IG and the spin column based Invisorb® Spin Virus RNA Mini Kit from STRATEC Molecular. 10 µl of the eluted RNA were amplified using the „dia Human metapneumovirus„ assay from Mikrogen Diagnostik (Neuried, Germany). Both extraction methods showed comparable CT values.*

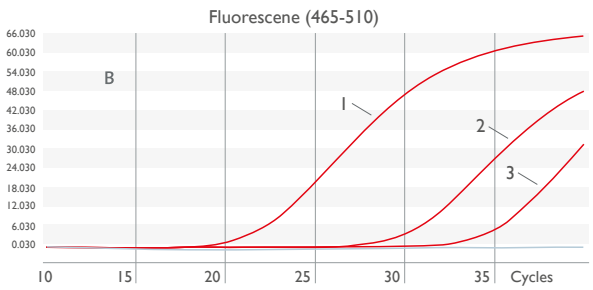
*1 - positive patient samples*
*2 - positive control*

## Fig. 2: Bacterial DNA isolation (Gram-positive bacteria)



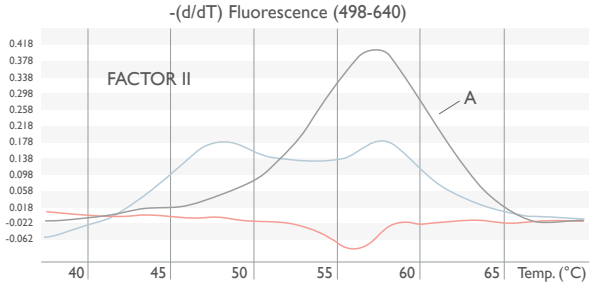

*Bacterial DNA was isolated from twelve potentially infectious patient samples (sputum samples, bacteria culture from swab) using the InviMag® Universal Kit/ IG. 10 µl of the eluted DNA were amplified using the „MutaPLATE M. tuberculosis„ real-time PCR assay from Immundiagnostik AG (Bensheim, Germany).*

*A: internal controls of all 12 samples – were amplified, without any inhibition*




*B: red - TBC positive patient samples*
*[swab (1); sputum (2) internal control (3)]*
*blue - TBC negative patient samples (valid negative results)*

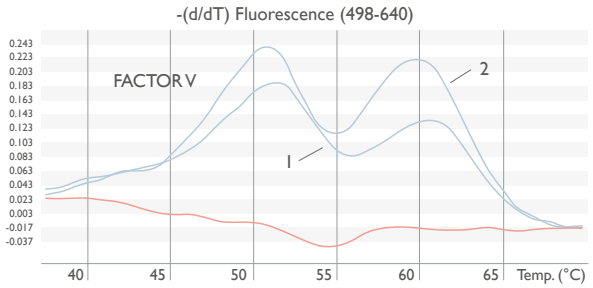
## Fig. 3: Genomic DNA isolation from blood samples




*Genomic DNA was isolated from 200 µl of human blood using the InviMag® Universal Kit/ IG. 10 µl of isolated DNA were amplified using the „RealStar Faktor II PCR Kit 3.0„ und „RealStar Faktor V PCR Kit 3.0„ from Altona Diagnostics (Hamburg, Germany).*

*Factor II: Patient sample - wild-type*
*Factor V: Patient sample - heterozygous for factor V*

*Factor II:*
*red - negative control*
*blue - positive control*
*grey - patient sample, wild-type (A)*




*Factor V:*
*red- negative control*
*blue - positive control (1)*
*blue - patient sample, heterozygous (2)*

## Tab. 1: Isolation of nucleic acids from twelve different pathogen containing samples in the same run

*DNA/RNA from different viruses and bacteria species were isolated using the InviMag® Universal Kit/ IG in the same run in parallel. For comparison an equivalent STRATEC Molecular spin kit was used with aliquots of the same sample. DNA/RNA eluates were analyzed via real-time PCR using the assays listed below. The results show comparable CT values.*

| Starting Material | Pathogen | Spin Kit | CT: Universal | CT:Spin | Assay |
|---|---|---|---|---|---|
| stool* | *Norovirus* | Invisorb® Virus RNA Mini Kit | 24.92 | 27.06 | RIDA GENE Norovirus [1)] |
| swab from urethra** | *Neisseria gonorrhoeae* | RTP® Bacteria DNA Mini Kit | 21.55 | 23.12 | Neisseria gonorrheae [2)] |
| swab** | *MRSA* | RTP® Bacteria DNA Mini Kit | 22.88 | 23.56 | GeneOhm MRSA Kits [3)] |
| stool* | *EHEC* | PSP® Spin Stool DNA Kit | 26.12 | 27.00 | RIDA GENE EHEC/EPEC rt PCR [1)] |
| urine | *Chlamydia trachomatis* | RTP® Bacteria DNA Mini Kit | 32.71 | 32.37 | Cobas Taqman CT V2.0 [4)] |
| stool* | *Clostridium difficile* | RTP® Bacteria DNA Mini Kit | 32.76 | 30.34 | RIDA GENE CD TOX A/B V [1)] |
| sputum**** | *Mycobacterium tuberculosis* | RTP® Mycobacteria Kit | 27.17 | 30.46 | MTB compl [2)] |
| sputum | *Metapneumo Virus* | Invisorb® Virus RNA Mini Kit | 23.79 | 24.00 | Metapneumo Virus [2)] |
| lyophilized cell lysate*** | *Influenza A/B (inkl. H1N1 & H5N1)* | Invisorb® Virus RNA Mini Kit | 24.73 | 24.03 | Influenza S&T RT PCR Kit2.0 [5)] |
| sputum | *Mycoplasma pneumophila* | RTP® Bacteria DNA Mini Kit | 34.32 | 29.58 | Mycoplasma & Pneumophila [2)] |
| swab** | *Adeno-Virus* | Invisorb® Virus DNA Mini Kit | 32.00 | 32.00 | Adeno-Virus [2)] |

**) supernatant from 50 mg stool, resuspended in 600 µl RNAse-free water, centrifuged at 2000 rpm for 2 min*
***) rinsed in 600 µl RNAse-free water*
****) resuspended in 1 ml bidest. water*
*****) sample is mixed with 20 vol % NAC Buffer and incubated for 10 min at 95°C*

*1: R-Biopharm*
*2: Mikrogen*
*3: BD*
*4: Roche Diagnostics*
*5: Altona Diagnostics*

*All data for the InviMag® Universal Kit/ IG kindly provided by M. Haesner, Medizinisches Labor Prof. Schenk/ Dr. Ansorge, Magdeburg, Germany.*

# 3. GENETIC TESTING FROM 2 ML OF BLOOD

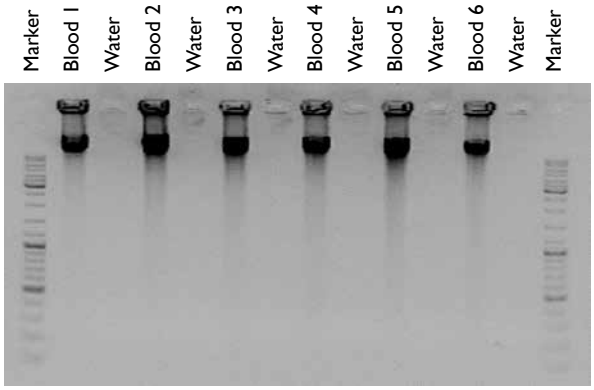
The InviMag® Blood DNA Maxi Kit/ IG enables fully automated, true walk-away purification of genomic DNA from human blood samples on the InviGenius® PLUS with sample volumes of up to 2 ml. Fresh or frozen whole blood treated with EDTA or citrate, but not with heparin, from common blood collection systems can be used.

Genomic DNA was extracted from 2 ml of six blood samples from different donors using the InviMag® Blood DNA Maxi Kit / IG on the InviGenius® PLUS in checkerboard series.

### Fig. 1 Nanodrop data

| Sample ID | Concentration in ng/µl | Ratio 260/280 | Ratio 260/230 | Yield in µg |
|---|---|---|---|---|
| Blood Sample 1 | 100.0 | 1.8 | 1.8 | 40.0 |
| water | 0.0 | - | - | 0.0 |
| Blood Sample 2 | 116.3 | 1.8 | 2.0 | 46.5 |
| water | 0.0 | - | - | 0.0 |
| Blood Sample 3 | 107.0 | 1.8 | 2.0 | 42.8 |
| water | 0.0 | - | - | 0.0 |
| Blood Sample 4 | 112.7 | 1.8 | 1.8 | 45.1 |
| water | 0.0 | - | - | 0.0 |
| Blood Sample 5 | 108.4 | 1.9 | 2.2 | 43.3 |
| water | 0.0 | - | - | 0.0 |
| Blood Sample 6 | 88.8 | 1.8 | 1.9 | 35.5 |
| water | 0.0 | - | - | 0.0 |

### Fig. 2 Agarose gel 1%, 5 µl Eluate



# SPECIFICATIONS AND ORDERING INFORMATION

## SPECIFICATIONS

**Technical Specifications**

| | |
|---|---|
| Sample volume | 200 to 4000 µl (protocol-specific) |
| Capacity | Up to 12 samples per run |
| Processing Time | 60 - 240 min (protocol-specific) |
| Magnetic rods | 12 (plus bottom magnets) |
| Heating temperature | Heat incubator, up to 95 °C |
| Computer | Integrated PC |
| Operating System | MS Windows |
| User interface | Touch screen |
| Ports / drives | USB, Ethernet, RS232 / 80 GB hard disc |
| Decontamination | UV irradiance |
| Dimensions | 75.6 x 80 x 76.5 cm, approx 76 kg |
| Type | Stand-alone table top instrument |
| Pipette tips | 1100 µl conductive disposable filter tips |
| Integrated barcode reader | 2/5 Interleaved, Code 39, Code 128, Codabar (>= 2.2:1) max. length of barcode: 20 digits, resolution down to 0.21 mm |
| Air displacement pipettor | Up to 1000 µl volume range<br>barometric and capacitive liquid level detection |
| Pipetting precision | Less than 2 % CV at 20 µl, less than 1 % CV at 100 µl |

### COMPREHENSIVE SERVICE AND SUPPORT BY A TRAINED TEAM

STRATEC Molecular's dedicated team of application and technical specialists will work with you to optimize the operation of the InviGenius® PLUS in your laboratory. We offer customized on- and off site training and flexible support agreements tailored to the needs of your laboratory.

# ORDERING INFORMATION

| Product name | Catalog number | Package size |
|---|---|---|
| InviGenius® Plus | 5011102000 | 1 unit |
| Waste Tray/ IG (disposable) | 5011100100 | 25 pieces |
| Sheaths | 5011100200 | 1000 pieces |
| Sheaths Bundle | 5011100300 | 10 x 48 pieces / rack |
| Conductive filter tips, 1100 µl | 5011100400 | 10 x 96 pieces / rack |

## Kits for use on the InviGenius® PLUS

| Product name | | Catalog number | Package size |
|---|---|---|---|
| InviMag® Universal Kit/ IG | CE | 2450120100 | 8 x 12 preps |
| InviMag® Blood DNA Mini Kit/ IG | CE | 2431120100 | 8 x 12 preps |
| InviMag® Blood DNA Maxi Kit/ IG | | 2431320100 | 8 x 12 preps |
| InviMag® SalivaGene DNA Kit/ IG | | 2435260100 | 8 x 12 preps |
| InviMag® FFPE DNA Kit/ IG | | 2432120100 | 8 x 12 preps |
| InviMag® Free Circulating DNA Kit/ IG | CE | 2439320400 | 8 x 12 preps |

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