Circulating Biomarkers:

New Solutions for RNA and DNA

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The products described in this webinar are intended for molecular biology applications. These products are not intended for the diagnosis, prevention or treatment of a disease.
Circulating Biomarkers: New solutions for RNA and DNA

Agenda

- Biomarker overview
  - Sample selection
  - Analyte selection
- Circulating miRNA biomarker discovery
- Circulating tumor DNA biomarker discovery
- Circulating mRNA biomarker discovery
- Summary of QIAGEN product offerings
- Questions
What is a biomarker?

- A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of antibodies</td>
<td>Elisa</td>
</tr>
<tr>
<td>Abnormal bp, blood cell counts, electrolyte</td>
<td>blood counts, pressure</td>
</tr>
<tr>
<td>Distinct histological indicators</td>
<td>microscopy</td>
</tr>
<tr>
<td>Abnormal liver function markers</td>
<td>biofluid assay</td>
</tr>
<tr>
<td>Presence of muscle injury protein markers</td>
<td>biofluid assay</td>
</tr>
<tr>
<td>Elevated kidney marker: serum creatinine</td>
<td>biofluid assay</td>
</tr>
<tr>
<td>Gene status or gene expression status</td>
<td>qPCR, NGS, Array, etc.</td>
</tr>
</tbody>
</table>
Cancer biomarker

**Personalized Medicine**

**Diagnostic**
- What type of cancer is it?

**Predictive**
- Is this the optimal drug for my cancer?

**Prognostic**
- Is it likely to develop this cancer?

**Pharmacodynamics**
- What’s the optimal dose for my body?

**Recurrence**
- Will the cancer return?
Noninvasive biomarker

In order to use a biomarker for diagnostics, the sample material must be as easy to obtain as possible:

- urine or saliva sample
- a drop of blood like those diabetes patients extract
- blood sample taken by a doctor
- CSF
- surgical biopsy
Samples:

Serum, Plasma, Cerebrospinal Fluid (CSF)

Analytes:

Cell-free miRNA, mRNA, DNA
What is blood?

RBC, WBC, platelets, CTC, ‘other cells’, extracellular?

- High levels of nucleases present in plasma
  - Freely circulating nucleic acids should be rapidly degraded
  - Surprisingly, stable nucleic acids can be detected in serum and plasma

$RBC$, $WBC$, platelets, other cells (e.g. circulating tumor cells)

Serum (post clotting)

Plasma (no-clotting)
Stable miRNAs in circulation

An evolving story

Exosomes/Microvesicles (MVs)

- MVs/exosomes are ~50-200 nm small vesicles excreted by all cells
- MVs/exosomes are found in all biofluids (e.g. blood)
- MVs/exosomes contain stable RNA (mRNA, miRNA, other small RNAs), DNA, and protein, protected from degradation by a lipid bilayer
- Contents are specifically packaged, mechanism of local and distant cellular communication

It’s the cargo that matters
Potential use of exosomes as analyte

Promise for disease detection and monitoring

- **Tumor profiling**
  - Surrogate diagnostics markers for biopsy profiling and possible utility to screen populations.

- **Prognosis and therapeutic monitoring**
  - Elevated level of exosomes in blood of patients with late-stage ovarian and lung cancer.

- **Profiling of patients**
  - Determine molecular signatures indicative of response versus non-response to therapy.

- **Therapeutics**
  - Delivery of exosomes payload to specific cells.

- **Less of a ‘needle in a haystack’**
  - $10^{10-12}$ exosomes/ml plasma, 1-10 CTC/ml blood. Impact for potential clinical utility.
Exosomes and liquid biopsies

miRNA example

- **Exosomal miRNA expression parallels originating tumor cell expression**
  - Taylor et al., Gynecol Oncol, 2010
  - Rabinowitz et al., Clin Lung Cancer, 2009
  - Logozzi et al., PLoS One, 2009

- **Minimal invasiveness**
  - Use exosomal miRNA profiling in the absence of tissue to and accurately reflect the tumor’s profile

- **Take home message**
  - Exosomal load assessment and exosomal molecular profiling hold great promise for disease detection and monitoring
Should you *only* look at exosomes?

No… **well**… sometimes!

- Potentially 90% of miRNAs in circulating are present in a non-membrane-bound form consistent with a ribonucleoprotein complex.
- At the same time, analyzing the exosome fraction could maximize signal-to-noise ratio of a potential biomarker providing better sensitivity.
Isolation of circulating miRNA and mRNA Analytes
Total RNA (miRNA + mRNA) Isolation from body fluids

miRNeasy Serum/Plasma Kit

Purification of circulating RNA from plasma, serum, CSF, urine, saliva, etc.

- Includes synthetic RNA control assay for normalization
- Minimal elution volume (14 µl)
- High-purity RNA suitable for all downstream applications
- Easy, robust procedures
- Automatable protocol
- **When possibly, avoid heparanized plasma**
  - If you *can’t avoid* heparinized samples, let me know! We have a solution!
Exosome purification & total RNA isolation from serum/plasma

exoRNeasy Serum/Plasma Maxi Kit

- Specifically enriches for RNA contained in vesicles
- Quickly isolates purified total RNA from microvesicles
- Efficiently isolates mRNA & miRNA from plasma/serum
- Enables use of high input volumes for sensitive detection of low abundance transcripts
- Processes multiple parallel samples with a convenient spin-column procedure
Intact vesicles are eluted from the exoEasy column

Scanning EM (20000x magnification) reveals higher purity with exoEasy

- Both preparations contain vesicle-shaped structures within an expected size range
- **UC**: Many smaller, unidentified structures/particles that do not match the expected size
- **exoEasy**: Intact vesicles with higher purity
Workflow

Separate Serum/Plasma
- Spin blood
- Transfer plasma/serum
- Filter
- Filtered plasma/serum

Isolate Exosomes
- Mix sample with Buffer XBP and bind to column
- Wash bound exosomes with Buffer XWP
- Lyse vesicles and elute with QIAzol

Isolate RNA
- Add chloroform to QIAzol eluate
- Recover aqueous phase and add ethanol
- Bind total RNA including miRNAs
- Wash 3x
- Elute
- Total RNA including miRNAs

- Microvesicle isolation
  - 20 minutes

- RNA isolation
  - 35 minutes
Isolation of Circulating DNA Analytes
Purification of free-circulating DNA from human body fluids

QIAamp Circulating Nucleic Acid Kit

**Purification of free-circulating DNA from human plasma, serum, urine, or other cell-free body fluids**

- Starting samples up to 5 ml
- Flexible elution volumes (20 µl to 150 µ)
- High-purity DNA suitable for all downstream applications
- Easy, robust procedures
- Automatable protocol
Circulating miRNA Biomarker Discovery
miScript PCR System

Complete miRNA quantification system

1. miScript II RT Kit
   - HiFlex Buffer: Unparalleled flexibility for miRNA and mRNA quantification from a single cDNA preparation
   - HiSpec Buffer: Unmatched specificity for mature miRNA profiling

2. miScript miRNA PCR Arrays
   - miRNome
   - Pathway-focused

3. miScript PreAMP Kit
   - Optional step for small or precious samples
   - Full miRNome profiling from as little as 1 ng RNA

4. Assays
   - miScript Primer Assays
   - miScript Precursor Assays
   - QuantiTect Primer Assays

5. miScript SYBR Green PCR Kit
   - QuantiTect SYBR Green PCR Master Mix
   - Universal Primer

6. miScript miRNA PCR Array data analysis software
   - Straightforward, free data analysis
Workflow

1. Isolate total RNA
2. Perform Reverse-transcription
3. Prepare PCR pre-mix
4. Load PCR arrays or plates
5. Perform real-time PCR
6. Analyze data
miRNA expression profiling: miScript miRNA PCR Arrays

miScript Primer Assays pre-dried in PCR plates

Pre-formatted, single use PCR arrays with wet-lab verified assays

- **miRBase Profiler miRNome Arrays**
  - Most species
  - Largest content
- **High Content (HC) Arrays**
  - Targeted miRNome profiling
- **Focused Arrays**
  - Bioinformatic driven profiling

Prep your PCR reaction mix → Load your plate → Run your real-time experiment!

No pipetting of individual primers!
miScript Primer Assay designs are extensively validated

What does assay validation mean to you? Quality!

1. **Primers have been designed using a state-of-the-art, proprietary algorithm.**

2. **All primer designs are bench validated in product development to ensure:**
   - Negligible background signal
   - Single, specific PCR product
   - Optimal dynamic range
   - Optimal reaction efficiency

3. **Any primer that fails validation is redesigned and retested.**
   - If the primer fails again, we do not offer it for sale

4. **All miScript miRNA PCR Arrays are quality controlled.**
New Product: miRBase Profiler miScript miRNA PCR Array

Choose *your* miRNome!

**miRBase Profiler Arrays**
- **Human**
  - Coverage through miRBase v21
  - 2402 primer assays!
- **Mouse**
  - Coverage through miRBase v21
  - 1765 primer assays!
- **Rat**
  - 653 primer assays
- **Dog**
  - 277 primer assays
- **Rhesus macaque**
  - 469 primer assays
- **Cow**
  - New!
  - 744 primer assays

**Benefits of miRBase Profiler Arrays**
- 100% validated assays
  - Each assay is bench validated
  - Each array is quality controlled
- Leading miRNome coverage
- Completely scalable!
  - Choose as many plates as you want...profile the v21 miRNome...profile only the v16 miRNome
- Contact product development if there is interest in other species!
Liver Tissue Profiling of a pool of ten healthy male liver tissues

miRBase Profiler

C_{T\text{, mean: pooled liver tissue}}

miRBase profiler miRNA Primer Assay

miScript

miRCURY

TaqMan

Number of human mature miRNAs
For each plate, the expressed miRNAs ($C_T < 35$) was determined. Note that plate 7 is a partially filled plate. Following this, the $C_T$ Mean and $C_T$ Median for the expressed miRNAs on each plate was calculated.
### Focused Arrays

- miFinder
- Cancer PathwayFinder
- Liver miFinder
- Brain Cancer
- Breast Cancer
- Ovarian Cancer
- Prostate Cancer
- Cancer Stem Cells
- Apoptosis
- Cardiovascular Disease
- Cell Differentiation & Development
- Diabetes
- Fibrosis
- Hypoxia Signaling Pathway
- Immunopathology
- Inflammatory Response & Autoimmunity
- Neurological Development & Disease
- Pain: Neuropathic & Inflammatory
- T-Cell & B-Cell Activation
- Tumor Suppressor miRNAs
- Serum & Plasma

### Benefits of Focused Arrays

- **100% validated assays**
  - Each assay is bench validated
  - Each array is quality controlled
- **Customizable**
- **Contact product development if there is interest in other species!**
miRNA expression profiling: miScript miRNA PCR Arrays (cont.)

Targeted miRNome expression profiling: High Content (HC) Arrays

- **miFinder 384HC**
- **Serum & Plasma 384HC**
- **Cancer PathwayFinder 384HC**
- **Liver miFinder 384HC**
- **Acetaminophen overdose is a common poisoning worldwide and can cause liver damage, potentially resulting in acute liver failure and death**
  - In the US and UK, acetaminophen overdose is the most common cause of acute liver failure

- **Scope of collaboration:**
  - Determine miRNA markers of acetaminophen poisoning
  - Distinguish acetaminophen poisoning from other liver syndromes

- **Experiment Workflow: Biomarker discovery**
  - **Phase 1:** Completed (377 miRNAs expressed)
    - Narrowed list from 1800 miRNAs
  - **Phase 2:** Completed (92 miRNAs of interest)
    - Derived initial 16 miRNA classifier signature
  - **Phase 3:** Ongoing
    - Refinement of initial classifier
    - Assessment of blind samples: Initial classifier has successfully grouped control and liver injury samples

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**Biomarker Discovery Workflow**

- **Phase I (determine expressed miRNAs):**
  - Pooled samples
  - miRNome profiling (or NGS)

- **Phase II (determine differentially expressed miRNAs):**
  - Individual profiling of samples (that went into pools)
  - Screen only expressed miRNAs (< 384-well plate)

- **Phase III (classifier refinement):**
  - Further individual sample profiling
  - Differentially Expressed miRNAs from Phase II
Phase 1: Determine expressed miRNAs

Survey the miRNA landscape for your system

- **54 plasma samples**: 27 control samples, 27 liver injury samples

- **Total RNA isolation**: miRNeasy Serum/Plasma Kit
  - **Note**: Perform QC at this step to ensure samples are devoid of inhibitors

- **Prepare random pools, 10 samples per pool**: 2 control pools, 2 patient pools

- **miRNA expression profiling**: miScript PCR System and Human miRNome (1800 assays)

### Which miRNAs were selected?

- miRNAs expressed in all 4 pools
- miRNAs expressed in 3 pools
- miRNAs expressed in 2 pools
- miRNAs expressed in 1 pool

~377 assays
Phase 2: Determine differentially expressed miRNAs

Secondary screen of individual samples from Phase 1

- **54 plasma samples**: 27 control samples, 27 liver injury samples
- **miRNA expression profiling**: miScript PCR System and expressed miRNAs (377 assays)
  - Replicate PCR reactions, 4 Fluidigm® Biomark™ runs. 40,000 data points, 4 days

Which miRNAs were differentially expressed?

Scatter plot

Volcano plot

Log$_{10}$ (Control Group $\Delta$CT)

Log$_{10}$ (Liver Injury Group $\Delta$CT)

- miR-122-5p
- miR-885-5p

Log$_2$ (FC of Liver Injury Group/Control Group)

- miR-885-5p
- miR-122-5p

Log$_{10}$ (P-value)
Phase 3: Statistical power

Develop training set of data on candidate markers

- **Samples:** Screen larger cohort of affected individuals
- **Assays:** Re-array differentially expressed miRNAs
  - Include invariant miRNAs (identified by NormFinder, etc.) for data normalization
- **Continually refine classifier model**
  - Original 54 samples, top 16 miRNAs
miRNA biomarker development

Important considerations

- Be novel! Initial whole miRNome screening = unique signatures!

  If the group would have only profiled the first two plates (roughly 768 mature miRNAs):

  - Only 64 of 92 differentially expressed or invariant miRNAs would have been assayed
    - 30% loss of data
    - Two invariant miRNAs would have been missed
  - 5 miRNAs from optimal 16 miRNA signature would not have been assayed
    - 3 of top 5 miRNAs from the signature would not have been assayed

- Verify miRNA signature on naïve samples

- Strong changes might be general indicators or even non-specific
  - Other liver disease? Stress markers?

- Relatively weak changes might add specificity

- High level of false positives is undesirable

- What’s next?
  - Revisit literature, Ingenuity® IPA, etc.
  - Screen other types of samples to help define specificity and refine signature.
miRNA expression profiling: miScript miRNA PCR Arrays (cont.)

Formats

**Prep** your PCR reaction mix → **Load** your plate → **Run** your real-time experiment!

*No pipetting of individual primers!*

**96-well**

- 84 miRNA assays
- 12 control assays

**384-well (4 x 96, 4 sample)**

- Assess 4 sample at one time!
  - 84 miRNA assays
  - 12 control assays
miRNA expression profiling: miScript miRNA PCR Arrays (cont.)

Formats

**Prep** your PCR reaction mix → **Load** your plate → **Run** your real-time experiment!

*No pipetting of individual primers!*

384-well (HC, 1 sample)

- 372 miRNA assays
- 12 control assays

Rotor-Disc 100

- 84 miRNA assays
- 12 control assays
miRNA expression profiling: miScript miRNA PCR Arrays (cont.)

Compatibility with commercial instruments

- 96-Well: 7000, 7300, 7500, 7700, 7900HT, ViiA 7
- FAST 96-Well: 7500, 7900HT, Step One Plus, ViiA 7
- FAST 384-Well: 7900HT, ViiA 7

- iPlex, MyiQ, MyiQ2, iQ5, CFX96, CFX384
- Opticon, Opticon 2, Chromo 4

- Mastercycler ep realplex 2/2S/4/4S

- LightCycler 480
- LightCycler 480 II

- Mx3000p, Mx3005p, Mx4000p

- TP-800

- RotorGene Q
Limiting samples: miScript PreAMP Kit

miRNome profiling from as little as 1 ng total RNA

- Highly multiplex, PCR-based preamplification
- Compatible with all miScript miRNA PCR Arrays and miScript Primer Assays
- Enables miRNA profiling experiments using very limited amounts of starting material
  - **Cell or tissues:** 1 ng total RNA
  - **Fluids:**
    - **Serum/plasma:** 50 µl or less
    - **Urine:** Any amount
    - **CSF:** Any amount
    - **Aqueous humor:** Any amount
  - *When in doubt, ‘miScript PreAMP’ it!*
New Product Release!

High-throughput miRNA expression profiling: miScript Microfluidics

- Isolation
- High-throughput miRNA Profiling
- Functionalization
What have we developed for the Fluidigm® BioMark™?

First, complete system for miRNA expression profiling on the BioMark
1. Reverse transcription (existing): miScript RT Kit
2. Preamplification (New): miScript Microfluidics PreAMP Kit
3. Real-time PCR reagents (New): miScript Microfluidics PCR Kit
4. Real-time PCR assays: miScript miRNA PCR Arrays (new) AND Assays (optimized)
   - Arrays are only ‘peal-and-use’ commercial assay offering for the Fluidigm BioMark
5. Data Analysis: Free data analysis using the ΔΔC_T method of relative quantification

What’s the bottom line advantage? A savings of time AND money!
Biomarker Discovery Example: 96 samples, 384 assays

96 Standard Real-Time PCR Plates
\[ \downarrow \]
2.25 hr per 384-well plate
\[ \downarrow \]
36,864 data points in 216 hr (27 days)

4 Fluidigm Real-Time PCR Chips
\[ \downarrow \]
5 hr per Chip
\[ \downarrow \]
36,864 data points in 20 hr (only 2 days!)
Circulating DNA Biomarker Discovery
qBiomarker Somatic Mutation

Workflow

1. Isolate DNA
2. Prepare PCR pre-mix
3. Load PCR arrays or plates
4. Perform real-time PCR
5. Analyze data
Principle behind qBiomarker Somatic Mutation

Amplification Refractory Mutation System (ARMS®)

ARMS Principle

Real-time PCR results

+ Mutation present
- Mutation absent
-/+ Mutation borderline

[Diagram showing ARMS Principle and real-time PCR results]
Sensitivity of qBiomarker

- qBiomarker PreAMP & qPCR: 400X more sensitive than Sanger
- Caveat: You have to know what you are looking for!
Sensitivity of qBiomarker

- **Assays**
  - Hydrolysis probe (FAM™ labeled)
  - Wet-bench validated
  - Optimized to work under standard cycling conditions

- **Arrays**
  - Dried-down assays
  - Pathway-focused & disease focused
  - Formats
    - 96-well/Rotor-Disc 100: 1 or 2 samples
    - 384-well: 1, 2, 4, or 8 samples
  - Compatible with any real-time instrument
Certain samples have small amounts of amplifiable DNA

<table>
<thead>
<tr>
<th>Freshly Isolated Sample</th>
<th>Small Sample</th>
<th>FFPE Sample</th>
<th>Serum Sample</th>
</tr>
</thead>
</table>

- Incorporate qBiomarker PreAMP into your workflow!
Certain samples have small amounts of amplifiable DNA

**Workflow**

1. Isolate circulating DNA
2. Perform qBiomarker PreAMP
3. Prepare PCR pre-mix
4. Load PCR arrays or plates
5. Perform real-time PCR
6. Analyze data

**PreAMP Principle**

- Enriches the amount of sample DNA at a specific gene
- qBiomarker PreAMP works exclusively with qBiomarker Somatic Mutation Assays/Arrays
- One extra PCR reaction is the gatekeeper to new discoveries!
qBiomarker PreAMP enables testing for circulating tumor DNA

Breast, colon, endometrial, and lung cancers

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Gene</th>
<th>AA change</th>
<th>Total Gene Copies/ml</th>
<th>Mutation Copies/ml</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>EGFR</td>
<td>p.L861Q</td>
<td>59971</td>
<td>35</td>
<td>0.06%</td>
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<tr>
<td>Lung</td>
<td>P53</td>
<td>p.R249W</td>
<td>48582</td>
<td>106</td>
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<tr>
<td>Endometrial</td>
<td>KRAS</td>
<td>p.G12A</td>
<td>16233</td>
<td>23</td>
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<tr>
<td>Breast</td>
<td>AKT1</td>
<td>p.E17K</td>
<td>22192</td>
<td>38</td>
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<tr>
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<td>AKT1</td>
<td>p.E17K</td>
<td>7301</td>
<td>31</td>
<td>0.43%</td>
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<tr>
<td>Colon</td>
<td>P53</td>
<td>p.R273C</td>
<td>14532</td>
<td>63</td>
<td>0.44%</td>
</tr>
</tbody>
</table>

**Experiment:**
- **Samples (normal and cancer serum):** 5 breast, 3 colon, 5 endometrial, 5 lung
- **Isolation:** Circulating DNA Isolation from 200-500 µl of serum
  - QIAamp Circulating Nucleic Acid Kit
- **PreAMP:** qBiomarker PreAMP
- **Real-time PCR:** qBiomarker Somatic Mutation Assays

Circulating tumor DNA is the most exciting new sample type to detect cancer mutations
- Mutation-containing DNA abundance is very low. qBiomarker PreAMP rectifies this!
Increasing the sensitivity of the largest collection of mutation assays in the world

- **qBiomarker Somatic Mutation** is the largest collection of cancer mutation assays
  - Over 1200 assays in over 100 genes
  - Custom design support

- **qBiomarker PreAMP** rescues samples for analysis such as circulating tumor DNA

- When considering different technologies, analysis methods, technical knowledge and ability, it is nice to know that a customer said, “Even my grandmother could do this.”
Circulating mRNA Biomarker Discovery

- Exosomes contain stable RNA including mRNA
- Isolation
  - exoRNeasy Serum/Plasma Maxi Kit
- Reverse-Transcription/PreAMP
  - RT² PreAMP cDNA Synthesis Kit
  - RT² PreAMP Pathway Primer Mix
- Real-time PCR
  - RT² Profiler PCR Arrays
  - RT² qPCR Primer Assays
Where can I find the products discussed today?

- www.qiagen.com
- www.qiagen.com/GeneGlobe
### QIAGEN’s miRNA portfolio

Your miRNA workflow, from sample to results!

#### Isolation
- miRNeasy Mini Kit, miRNeasy Micro Kit
- miRNeasy 96 Kit
- miRNeasy FFPE Kit
- miRNeasy Serum/Plasma Kit
- Modified miRNeasy Mini Kit for plant tissues
- PAXgene Tissue miRNA Kit
- PAXgene Blood miRNA Kit
- Supplementary protocol for miRNA from Plasma and Serum

#### Quantification and profiling
- miScript II RT Kit
- miScript Plant RT Kit
- miScript PreAmp Kit
- miScript SYBR Green PCR Kit
- miScript miRNA PCR Arrays
- miScript Microfluidics for Fluidigm

#### Functionalization
- HiPerFect Transfection Reagent
- Attractene Transfection Reagent
- miScript miRNA Mimics
- miScript miRNA Inhibitors
- Custom miScript miRNA Mimics
- Miic and inhibitor controls
- miScript Primer Assay
- miScript Target Protector
- miScript Precursor Assay
- miScript miRNA Inhibitor 96 and 384 Plates and Sets

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**QIAGEN Service Core**  
**QIAcube**  
**QI Agility**  
**Rotor-Gene Q**
QIAGEN’s mRNA detection portfolio

Your gene expression analysis workflow, from sample to results!

**Isolation**

- RNeasy Mini Kit
- RNeasy Microarray Tissue Mini Kit
- RNeasy FFPE Kit
- RNeasy Micro Kit
- PAXgene Blood RNA Kit

**Quantification and profiling**

- RT² First Strand cDNA Kits
- RT² qPCR Master Mixes
- RT² Profiler PCR Arrays (Profiling)
- RT² qPCR Primer Assays
- GeneGlobe Data Analysis Center

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**High-throughput**

- QIAcube
- QIAgility
- Rotor-Gene Q
Questions?

Thank you for attending today’s webinar!

Jonathan Shaffer, Ph.D.

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