Ultra-sensitive NGS-based liquid biopsy technology in companion diagnostics

QIAGEN & Sysmex Inostics
August 25, 2021
Disclaimer

Safe Harbor Statement: This presentation contains both historical and forward-looking statements. All statements other than statements of historical fact are, or may be deemed to be forward looking statements within the meaning of Section 27A of the U.S. Securities Act of 1933, as amended, and Section 21E of the U.S. Securities Exchange Act of 1934, as amended. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or unknown risks or uncertainties materialize, actual results could vary materially from our own expectations and projections. Some of the factors that could cause actual results to differ include, but are not limited, to the following: general industry conditions and competition; risks associated with managing growth and international operations (including the effects of currency fluctuations, regulatory processes and dependence on logistics), variability of operating results and allocations between customer classes, and the commercial development of markets for our products to customers in academia, pharma, applied testing and molecular diagnostics; changing relationships with customers, suppliers and strategic partners; competition; rapid or unexpected changes in technologies; fluctuations in demand for QIAGEN’s products (including factors such as general economic conditions, the level and timing of customers’ funding, budgets and other factors); our ability to obtain regulatory approval of our products; technological advances of our competitors and related legal disputes; difficulties in successfully adapting QIAGEN’s products to integrated solutions and producing such products; the ability of QIAGEN to identify and develop new products and to differentiate and protect our products from competitor products; market acceptance of QIAGEN’s new products and the integration of acquired technologies and businesses. For further information, please refer to “Risk Factors” section of reports that QIAGEN has filed with, or furnished to, the U.S. Securities and Exchange Commission (SEC). We undertake no obligation, and do not intend, to update these forward-looking statements as a result of new information or future events or developments unless and to the extent required by law.

Regulation G: QIAGEN reports adjusted results, as well as results on a constant exchange rate (CER) basis, and other non-U.S. GAAP figures (generally accepted accounting principles), to provide additional insight on performance. In this presentation, adjusted results include adjusted net sales, adjusted operating expenses, adjusted EBITDA, adjusted diluted EPS and free cash flow. Adjusted results are non-GAAP financial measures QIAGEN believes should be considered in addition to reported results prepared in accordance with GAAP, but should not be considered as a substitute. QIAGEN believes certain items should be excluded from adjusted results when they are outside of its ongoing core operations, vary significantly from period to period, or affect the comparability of results with its competitors and its own prior periods. Please see the Appendix provided in this presentation “Reconciliation of Non-GAAP to GAAP Measures” for reconciliations of historical non-GAAP measures to comparable GAAP measures and the definitions of terms used in the presentation. QIAGEN does not reconcile forward-looking non-GAAP financial measures to the corresponding GAAP measures due to the high variability and difficulty in making accurate forecasts and projections that are impacted by future decisions and actions. Accordingly, reconciliations of these forward-looking non-GAAP financial measures to the corresponding GAAP measures are not available without unreasonable effort. However, the actual amounts of these excluded items will have a significant impact on QIAGEN’s GAAP results.
Today’s speakers

Dr. Reinhard Ortmann, Director Companion Diagnostics, QIAGEN
• Leads all commercial collaborations with a strong sense of partnership

Dr. Johannes Fredebohm, Head of Research & Innovation, Sysmex Inostics
• Drives SafeSEQ technology development, guided by a strong desire to improve patient lives

Dr. Frederick S. Jones, Sr Director, Life Science Medical Affairs, Sysmex Inostics
• Patient-centric approach to clinical development of several LDTs and FDA-approved IVDs
Agenda

- Embracing opportunity through the QIAGEN-Sysmex Inostics partnership
- The Power of SafeSEQ: Technology and performance overview
- Realizing the clinical value of ultra-sensitive technology
Agenda

- Embracing opportunity through the QIAGEN-Sysmex Inostics partnership
- The Power of SafeSEQ: Technology and performance overview
- Realizing the clinical value of ultra-sensitive technology
Embracing opportunity through the QIAGEN-Sysmex partnership

QIAGEN
CDx development & commercial excellence

Sysmex Inostics
Pioneers of the clinical liquid biopsy revolution
QIAGEN
CDx development & commercial excellence

Oncology assays, PCR & NGS

- *therascreen*: Top portfolio of solid tumor companion diagnostics
- *ipsogen*: Full range of assays for clinical diagnosis and monitoring in blood cancer
- *QIAseq*: Wide portfolio of NGS technologies and panels including rapid custom development

CDx co-development project

- >30 master collaboration agreements with pharma and biotech companies
- Proven success in delivering CDx to the market with FDA and CE-IVD status
- Global CDx partnerships through:
  - PCR programs
  - Digital PCR programs
  - NGS programs

QIAGEN oncology CDx FDA approvals

<table>
<thead>
<tr>
<th>Assay</th>
<th>Year</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>2012</td>
<td>Lilly</td>
</tr>
<tr>
<td>EGFR</td>
<td>2013</td>
<td>Boehringer Ingelheim</td>
</tr>
<tr>
<td>KRAS</td>
<td>2014</td>
<td>AMGEN</td>
</tr>
<tr>
<td>EGFR</td>
<td>2015</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>EGFR</td>
<td>2018</td>
<td>Pfizer</td>
</tr>
<tr>
<td>FGFR</td>
<td>2019</td>
<td>Janssen</td>
</tr>
<tr>
<td>BRAF V600E</td>
<td>2020</td>
<td>Pfizer</td>
</tr>
<tr>
<td>KRAS</td>
<td>2021</td>
<td>AMGEN</td>
</tr>
</tbody>
</table>

**PIK3CA**
- Breast

**FGFR**
- Urothelial

**BRAF V600E**
- Colorectal

**KRAS**
- NSCLC
Sysmex Inostics
Pioneers of the clinical liquid biopsy revolution

BEAMing developed as first dPCR for ctDNA analysis
Dressman 2003

SafeSEQ developed as first UMI-based NGS for ctDNA analysis
Kinde 2011 PNAS

cDNA monitoring disease dynamics
Diehl 2008 Nature Medicine

PIK3CA concordance
Higgins et al. 2012 Clinical Cancer Research
Emerging RAS
Diaz, Nature Medicine 2012

ctDNA pan-cancer survey
Bettegowda et al. 2014 Science Translational Medicine

I/O monitoring
Rowe et al. 2018 Molecular Oncology

EGFR T790M
Oxnard et al. 2016 Journal of Clinical Oncology
ESR1 heterogeneity
Spoerke et al. 2016 Nature Communications

SafeSEQ NGS launched

ctDNA monitoring disease dynamics
Diehl 2008 Nature Medicine

PIK3CA concordance
Higgins et al. 2012 Clinical Cancer Research
Emerging RAS
Diaz, Nature Medicine 2012

ctDNA pan-cancer survey
Bettegowda et al. 2014 Science Translational Medicine

I/O monitoring
Rowe et al. 2018 Molecular Oncology

EGFR T790M
Oxnard et al. 2016 Journal of Clinical Oncology
ESR1 heterogeneity
Spoerke et al. 2016 Nature Communications

SafeSEQ NGS launched
A partnership intended to accelerate oncological discoveries

<table>
<thead>
<tr>
<th>Translational research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra-sensitive ctDNA technology</td>
</tr>
<tr>
<td>Detect ctDNA at levels an order of magnitude below pan-cancer assays, as low as 5 mutant molecules detected</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expert partners in drug development</td>
</tr>
<tr>
<td>Over two decades combined BioPharma clinical trial support experience</td>
</tr>
<tr>
<td>Sysmex Inostics CLIA-validated lab</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CDx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development and commercial leadership</td>
</tr>
<tr>
<td>Proven track record supporting regulated molecular assays globally</td>
</tr>
</tbody>
</table>
Agenda

- Embracing opportunity through the QIAGEN-Sysmex Inostics partnership
- The Power of SafeSEQ: Technology and performance overview
- Realizing the clinical value of ultra-sensitive technology
SafeSEQ: Empowering discoveries in oncology

No molecule left behind

SafeSEQ technology is optimized to detect low-frequency mutant molecules in plasma with high specificity

Ultra-sensitive ctDNA NGS detection

- Aid cancer drug development
- Monitor therapeutic efficacy
- Identify treatment resistance
- Detect minimal residual disease (MRD)

SafeSEQ detects 5 mutant molecules in a background of 10,000 wild-type molecules (0.05% MAF)
SafeSEQ workflow

Ultra-sensitive detection of low-level mutant molecules across the entire workflow

**Blood collection**
- Validated pre-analytics
- Optimizes signal-to-noise

**DNA extraction & quantification**
- Sufficient DNA input
- Maximizes ctDNA detection

**Preparation of sequencing libraries**
- High-efficiency chemistry
- Ensures no molecule is left behind

**Sequencing**
- Unique molecular identifier
- Increases specificity and sensitivity

**Data analysis**
- Proprietary Software
- Optimized for low-frequency mutation calling

**Reporting**
- Easy-to-interpret patient and QC reports
- Delivers the information you need

1st Day

2nd Day
SafeSEQ workflow

Ultra-sensitive detection of rare mutant molecules across the entire workflow

Blood collection → DNA extraction & quantification → Library preparation using SafeSEQ → Sequencing → DNA analysis & reporting

Circulating plasma-DNA
Unique identifier (UID) assignment

Index PCR (for sample identification)

UID families

What differentiates SafeSEQ?

Designed specifically for ctDNA

*Not a tissue sequencing method adapted for plasma*

Amplification-based sequencing technology

*Continuing the digital approach of BEAMing*

---

Digital analysis using molecular barcoding reduces risk of false positives
SafeSEQ demonstrates ultra-high sensitivity independent of DNA input

5-7 mutant molecules can be reliably detected
Designed to leave no molecule behind

**SafeSEQ**

Designed to not lose input molecules

100% of starting molecules are analyzed with SafeSEQ

**Ligation/hybrid-capture based NGS**

Loss of input molecules results in limited detectability

False Negative

40% of molecules could be lost during sample prep prior to NGS analysis
SafeSEQ performance characterization

**SafeSEQ is as sensitive as BEAMing**

R² = 0.9868

**SafeSEQ is more sensitive than competitive assays**

5 – 6 fold
SafeSEQ is ideal for BioPharma

Superior therapy selection and monitoring, and MRD detection

- **SafeSEQ**
  - Ultra-sensitive therapy selection
  - Therapeutic monitoring
  - Minimal residual disease (MRD) detection

- **OncoBEAM**
  - Ultra-sensitive therapy selection
  - Limited therapeutic monitoring
  - Limited MRD detection

- **qPCR**
  - Therapy selection

- **Pan-cancer NGS**
  - Therapy selection
  - R&D biomarker discovery

**Graphical Representation**

- **Clinically-relevant mutations**
- **Sensitivity**

**Legend**

- **SafeSEQ**
- **OncoBEAM**
- **qPCR**
- **Pan-cancer NGS**
Agenda

- Embracing opportunity through the QIAGEN-Sysmex Inostics partnership
- The Power of SafeSEQ: Technology and performance overview
- Realizing the clinical value of ultra-sensitive technology
  - Breast cancer
  - HPV cancer
  - Case studies
Clinical benefits of ultra-sensitive ctDNA detection

Circulating tumor DNA (ctDNA) is differentiated from circulating normal DNA based on the presence of somatic mutations:
- Somatic mutations are highly specific
- Every cancer has at least one mutation

ctDNA a surrogate for tumor burden:
- Clearance of plasma mutations to indicate favorable outcome
- Predict durable responses to therapy
- Detect resistance markers

Mari et al, Cancers 2019, 11(6), 774
Clearance of ctDNA (EGFR mutations) indicates favorable response to treatment

Clearance of plasma EGFR mutations as a predictor of outcome on osimertinib in the AURA trial

<table>
<thead>
<tr>
<th>Group</th>
<th>Median PFS (95% Cl)</th>
<th>ORR</th>
<th>P-value (log rank test)</th>
<th>Hazard ratio (95% Cl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance of plasma EGFR mutations at 6 weeks</td>
<td>n=92 10.8 months 95% Cl 9.3, 12.7</td>
<td>74%</td>
<td>&lt;0.0001</td>
<td>2.64 (1.81, 3.84)</td>
</tr>
<tr>
<td>Detectable plasma EGFR mutations at 6 weeks</td>
<td>n=51 4.2 months 95% Cl 4.1, 6.8</td>
<td>41%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

High sensitivity matters

SafeSEQ and BEAMing have analytical sensitivities of ≥ 0.02-0.06%

- **Distribution of RAS MAFs in mCRC patients**
  - 0.02-0.1%: 38%
  - >0.1-1%: 14%
  - >1%: 35%
  - >5%: 13%

- **Distribution of EGFR MAFs in EGFR-mutant NSCLC patients with T790M+ resistance**
  - 0.02-0.1%: 36%
  - 0.1-1%: 22%
  - >1%: 15%
  - >5%: 27%

- **Distribution of PIK3CA MAFs in HR+/HER- recurrent Breast Cancer patients**
  - 0.02-0.1%: 22%
  - 0.1-1%: 22%
  - >1%: 32%
  - >5%: 23%

48% of patients with MAFs <1%

42% of patients with MAFs <1%

45% of patients with MAFs <1%

# Available SafeSEQ panels

## CLIA-validated panels

<table>
<thead>
<tr>
<th>SafeSEQ panel</th>
<th>Clinically relevant gene regions</th>
<th>Clinical intended uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAS RAF pathway</td>
<td>AKT1, BRAF, KRAS, NRAS, PIK3CA</td>
<td>• Therapy selection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Therapeutic monitoring</td>
</tr>
<tr>
<td>HPV cancers</td>
<td>HPV 16, HPV 18</td>
<td>• Therapy selection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Therapeutic monitoring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Recurrence surveillance</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>AKT1, ERBB2, ESR1, KRAS, PIK3CA, TP53</td>
<td>• Therapy selection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Therapeutic monitoring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Recurrence surveillance</td>
</tr>
</tbody>
</table>

**Plasma-SeqSensei™ RUO Kit, EU ONLY**

Colorectal Cancer

Melanoma

Non small cell lung cancer

Thyroid Cancer

Breast Cancer
Sensitive ctDNA analysis:
Clinical applications in breast cancer
SafeSEQ Breast Cancer Panel (BCP)

Focused coverage of highly clinically relevant mutations

SafeSEQ BCP offers expanded genomic coverage while maintaining ultra-high sensitivity of mutation detection in plasma, making it a well-suited tool to detect minimal residual disease.
SafeSEQ BCP clinical intended uses

**Primary clinical intended uses**
(Metastatic ER+/HER2- Breast Cancer)

1. **Therapy selection (ESR1, PIK3CA, AKT1)**

2. **Therapy response monitoring**
   - ctDNA kinetics as an early indicator of response
   - Identification of resistance mutations (ESR1, KRAS, HER2)

3. **Recurrence detection and disease surveillance**

Diagnosis

Therapeutic biomarker testing (ESR1, PIK3CA, AKT1)

First-line therapy

Therapeutic biomarker testing (ESR1, PIK3CA, AKT1)

Second-line therapy

Tumor recurrence
SafeSEQ has equivalent sensitivity to OncoBEAM

**SafeSEQ Breast Cancer Panel:**
AKT1, ERBB2, ESR1, KRAS, PIK3CA, TP53

- 35 breast cancer patient samples in addition to contrived samples were tested using PSS and OncoBEAM
- Limit of detection (95% CI) for SafeSEQ Breast Cancer Panel: **6 mutant molecules**
  - Corresponds to **0.03% MAF** for 20,000 genomic copies DNA input (~66 ng)

Hope Rugo et al. Presented at AACR 2019
ctDNA can inform treatment selection

Progression and resistance monitoring

Mutation snapshot in newly diagnosed ER+/HER2- patient

PIK3CA 25%

Molecular testing not routinely performed in newly diagnosed ER+/HER2- patients

Mutation snapshot at progression

PIK3CA 25%

PIK3CA + 20%

ESR1 40%

Alpelisib

Alpelisib + ESR1 Tx?

ESR1 Tx

PIK3CA testing recommended in 2nd line and will eventually include ESR1 when therapy is approved
Almost 40% of patients progressing after treatment with Palbociclib (CDK4/6i) + combination with Fulvestrant or Tamoxifen have trackable biomarkers like PIK3CA and ESR1 that can be used in clinical development.

69 patients: 52 ctDNA positive, 17 ctDNA negative

**Most Commonly Mutated Genes in cfDNA**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Total number of mutations found in all patients</th>
<th>Total number of patients with mutation</th>
<th>Patients with 1 mutation</th>
<th>Patients with &gt;1 mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIK3CA</td>
<td>43</td>
<td>27 (39%)</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td>ESR1</td>
<td>40</td>
<td>24 (35%)</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>TP53*</td>
<td>46</td>
<td>30 (43%)</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>ERBB2</td>
<td>4</td>
<td>3 (4%)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>AKT1</td>
<td>4</td>
<td>4 (6%)</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>KRAS*</td>
<td>1</td>
<td>1 (1.4%)</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

*Based on variant allele frequencies relative to other mutations, nine (9) TP53 mutations and one (1) KRAS mutation may be from clonal hematopoiesis
ESR1 mutation detection is essential for drugs targeting ER+/HER2- patients in clinical trials

Tissue testing for ESR1 not suitable due to molecular heterogeneity

Blood-based testing maximizes identification of patients

3% detection rate

40% can be detected longitudinally

Oesterreich, Davidson, Nature Genetics 2013
ER+/HER2- primary breast cancer patient management

- Diagnosis
- OR
- high risk
- Neoadjuvant Chemotherapy
- Surgery (± radiation)
- Hormone therapy (± chemotherapy)
- 5 years? >5 years?
- Lifetime risk of recurrence

- What happens **after successful treatment**?
- How do we determine **who is cured**?
- **Lifetime surveillance** for patients?
SafeSEQ technology for sensitive MRD detection in TNBC

SafeSEQ ultra-sensitive ctDNA detection to correlate the presence or absence of ctDNA post-neoadjuvant treatment with presence of disease at surgery

CTDNA POSITIVE -> MINIMAL RESIDUAL DISEASE

CTDNA NEGATIVE -> No Minimal Residual Disease
Sensitive HPV cfDNA analysis: Clinical applications in Head and Neck Squamous Cell Carcinoma (HNSCC)
SafeSEQ circulating HPV assay (HPV-SEQ)

Enable precise tracking of disease burden and response to therapy

Non-invasive blood test:
Sensitive detection of HPV 16 and HPV 18 in plasma across a broad dynamic range (over 5 orders of magnitude).
- HPV+ Head and Neck Squamous Cell Carcinoma (HNSCC)
- Anal Squamous Cell Carcinomas (ASCC)
- Cervical Cancer

Clinical applications:
- Monitor disease burden during therapy
- Assess response to treatment (support treatment escalation/de-escalation strategies)
- Post-treatment surveillance to detect disease recurrence
Ultra-sensitive detection and quantification of HPV DNA in the plasma of patients with oropharyngeal squamous cell carcinoma (OPSCC) enrolled in the OPTIMA 2 treatment de-escalation trial

- Data displayed in the graph to the left represents changes in cfHPV-DNA levels from 25 patients undergoing induction therapy in the OPTIMA 2 trial.

- Plasma samples were collected from patients prior to induction therapy and 6-9 weeks after beginning therapy.

- HPV-SEQ showed robust quantitative detection of HPV 16 and HPV 18 across a broad dynamic range over five orders of magnitude.

- Decreases in cfHPV-DNA levels were consistent with tumor response (determined radiographically post-therapy) observed in 24/25 (96%) patients.
Patient management opportunities when using a highly sensitive ctDNA HNSCC assay

Genes covered: CDKN2A, EGFR, ERBB2, FGFR3, HRAS, KRAS, NOTCH1, PIK3CA, PTEN, TP53

- Quickly and accurately identify patients appropriate for treatment.
- Detect residual disease and assess response to therapy (including immunotherapy) using rapid and real-time non-invasive assay.
- Avoid needless therapies (over-treatment) in the neoadjuvant and adjuvant settings.
- Allow for individualized decisions to optimally refine treatment strategies.
- Serve as useful intermediate endpoints and improve efficiency of clinical trials.
Clinical cases showing value of SafeSEQ ctDNA detection
Case study 1: BRAF-targeted therapy monitoring in NSCLC

- ctDNA decrease after starting 1st line treatment; complete ctDNA clearance is not observed.
  - Persistent ctDNA predictive of treatment non-response

- Subsequent ctDNA increase is consistent with disease progression observed by imaging

- BRAF clone is present at lower levels compared to PIK3CA after treatment with BRAF-targeted therapy
Case study 2: Treatment monitoring in CRC

- Initial ctDNA decrease on first line therapy is consistent with radiographic treatment response (decrease in tumor volume)
- Lack of full ctDNA clearance on treatment (ctDNA persistence) is predictive of disease progression
- Dramatic increase in ctDNA beginning after day 200 is consistent with disease progression, which precedes increase in tumor volume measurements by ~5 months
- Mutations detected in plasma by SafeSEQ: APC E582*, APC R1386*, EP300 Q226_Q2267>Q, TP53 R175H, KRAS G13D (plotted below)
Immunotherapy therapy response and monitoring

• **Goal:** Assess feasibility of ctDNA as an indicator of tumor burden in patients with advanced solid tumors treated with immunotherapy.

• **Clinical questions:**
  1. Are early, dynamic changes in ctDNA levels predictive of benefit to immunotherapy?
  2. Do dynamic changes throughout the course of treatment add to the clinical utility of ctDNA-based monitoring?

• **Hypotheses:**
  1. Early changes in ctDNA levels precede radiographic response.
  2. Failure to clear ctDNA early in treatment predicts lack of durable benefit.
Case 3: Immunotherapy monitoring in NSCLC

- ctDNA clearance early after starting nivolumab treatment predicts durable response
- Sustained ctDNA clearance during nivolumab treatment is consistent with durable response determined by imaging
- Mutations detected by SafeSEQ: ATM E688*, DAXX R306*, TP53 splice site 673-2A>T
Conclusions

- ctDNA is often present at very low levels (<0.1% MAF), which necessitates highly sensitive detection methods.

- SafeSEQ enables expanded genomic coverage, while demonstrating equivalent sensitivity to OncoBEAM dPCR.

- SafeSEQ assays are optimally designed to identify tumor mutations across cancer types for a range of intended uses:
  - Better inform therapy selection
  - Dynamically monitor tumor response
  - Identify resistance mutations
  - Detect minimal residual disease
BioPharma opportunity through the QIAGEN-Sysmex partnership

Faster trials
Cost-effective
Earlier to market
Impact more lives
Thank you.
If you have any questions, please contact:

Reinhard.Ortmann@qiagen.com
Q&A