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

QIAGEN & Sysmex Inostics

August 25, 2021

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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

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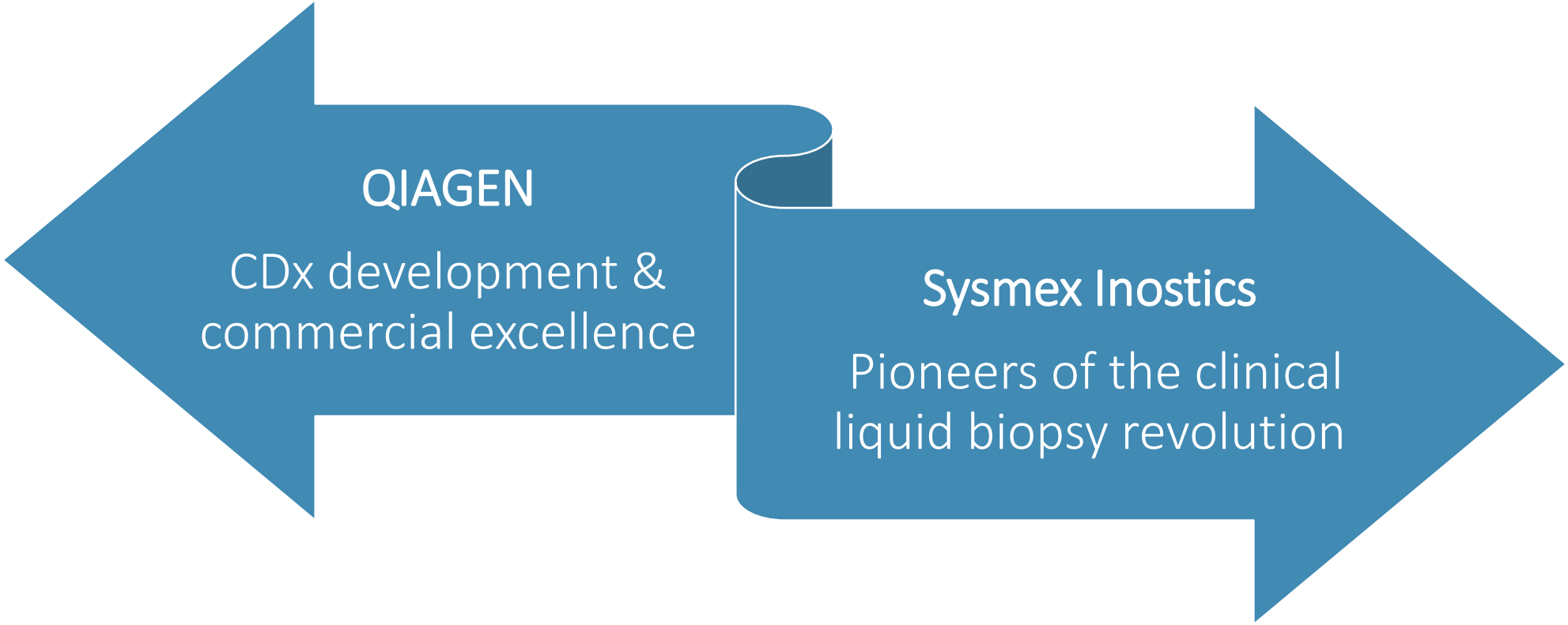
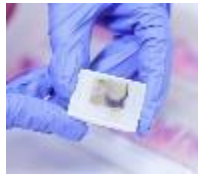
Embracing opportunity through the QIAGEN-Sysmex partnership



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

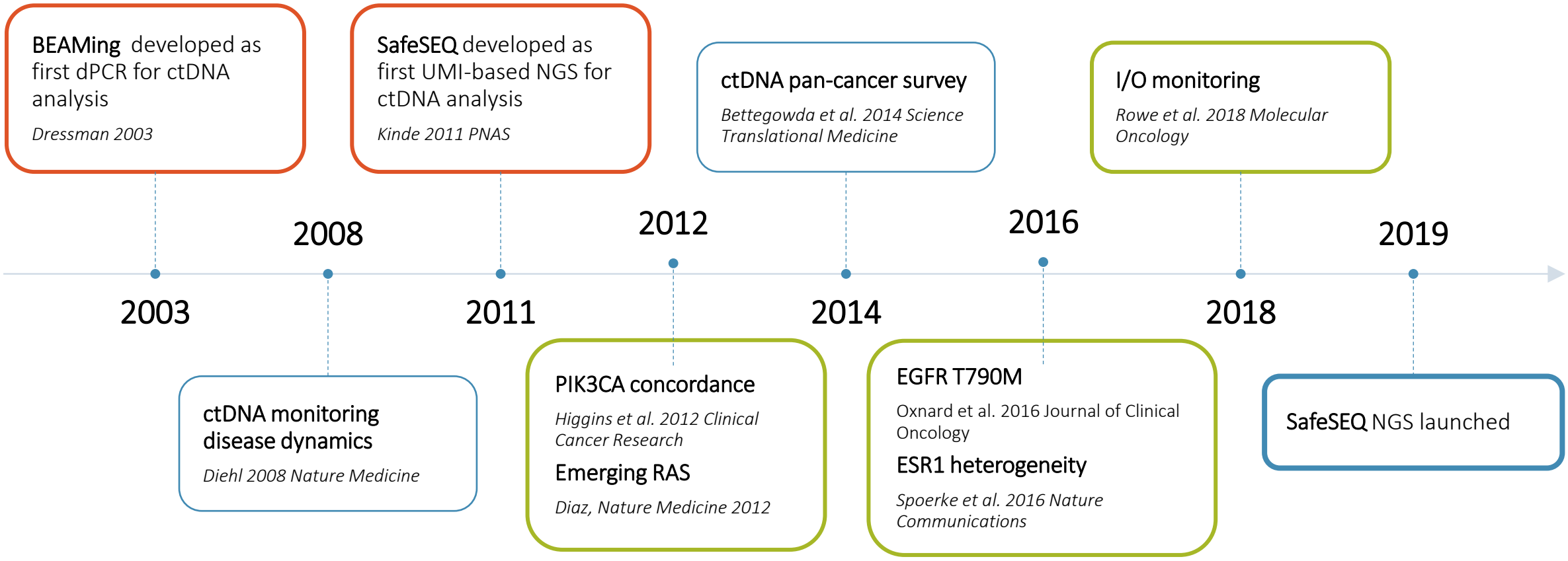
Global CDx partnerships through:

- PCR programs
- Digital PCR programs
- NGS programs

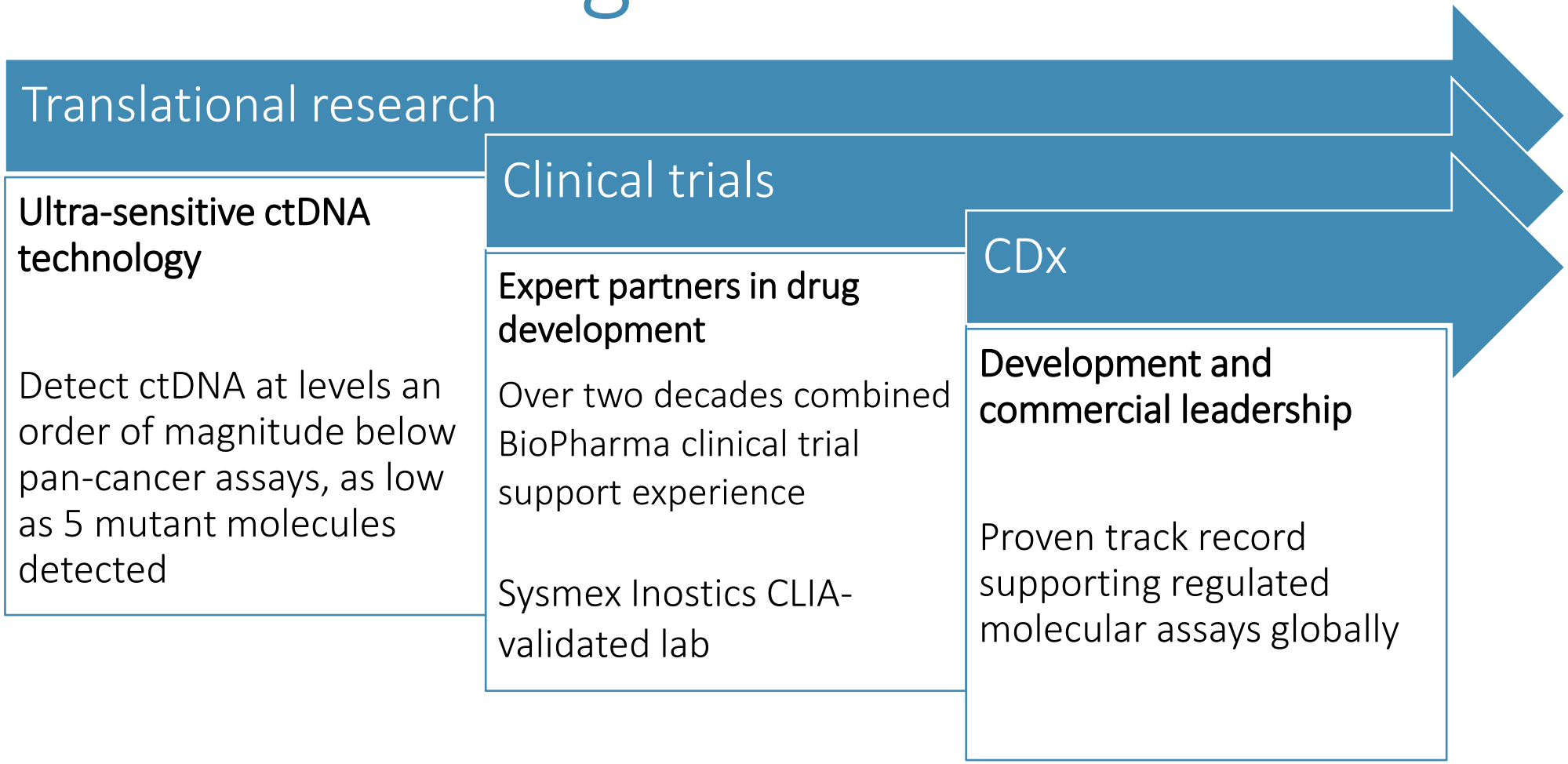
QIAGEN oncology CDx FDA approvals

2012	2013	2014	2015	2018	2019	2020	2021
Lilly	Boehringer Ingelheim	AMGEN	AstraZeneca	Pfizer	NOVARTIS	Pfizer	AMGEN
KRAS Colorectal	*EGFR* Lung	*KRAS* Colorectal	*EGFR* Lung	*EGFR* Lung	*PIK3CA* Breast Janssen *FGFR* Urothelial	*BRAF* V600E Colorectal	KRAS NSCLC

Sysmex Inostics
Pioneers of the clinical liquid biopsy revolution



A partnership intended to accelerate oncological discoveries



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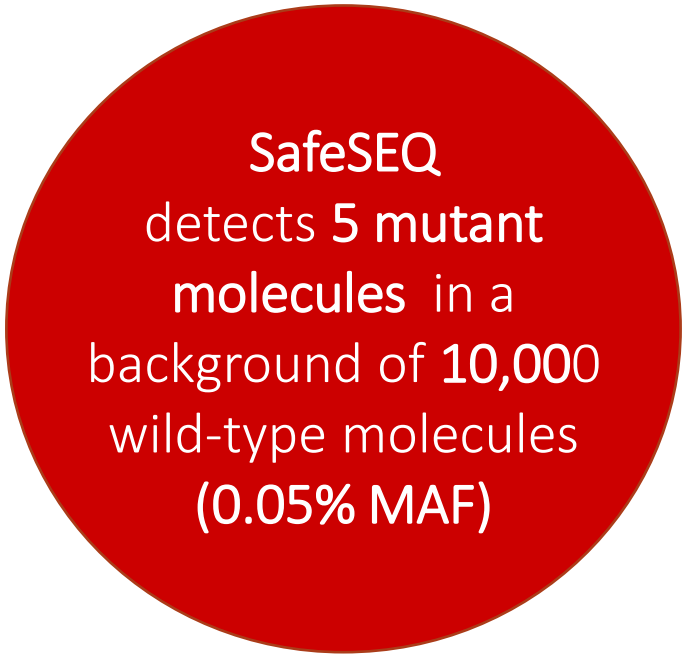
- Embracing opportunity through the QIAGEN-Sysmex Inostics partnership
- The Power of SafeSEQ: Technology and performance overview
- Realizing the clinical value of ultra-sensitive technology

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 workflow

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

Blood collection	DNA extraction & quantification	Preparation of sequencing libraries	Sequencing	Data analysis	Reporting
Validated pre-analytics	Sufficient DNA input	High-efficiency chemistry	Unique molecular identifier	Proprietary Software	Easy-to-interpret patient and QC reports
Optimizes signal-to-noise	Maximizes ctDNA detection	Ensures no molecule is left behind	Increases specificity and sensitivity	Optimized for low-frequency mutation calling	Delivers the information you need



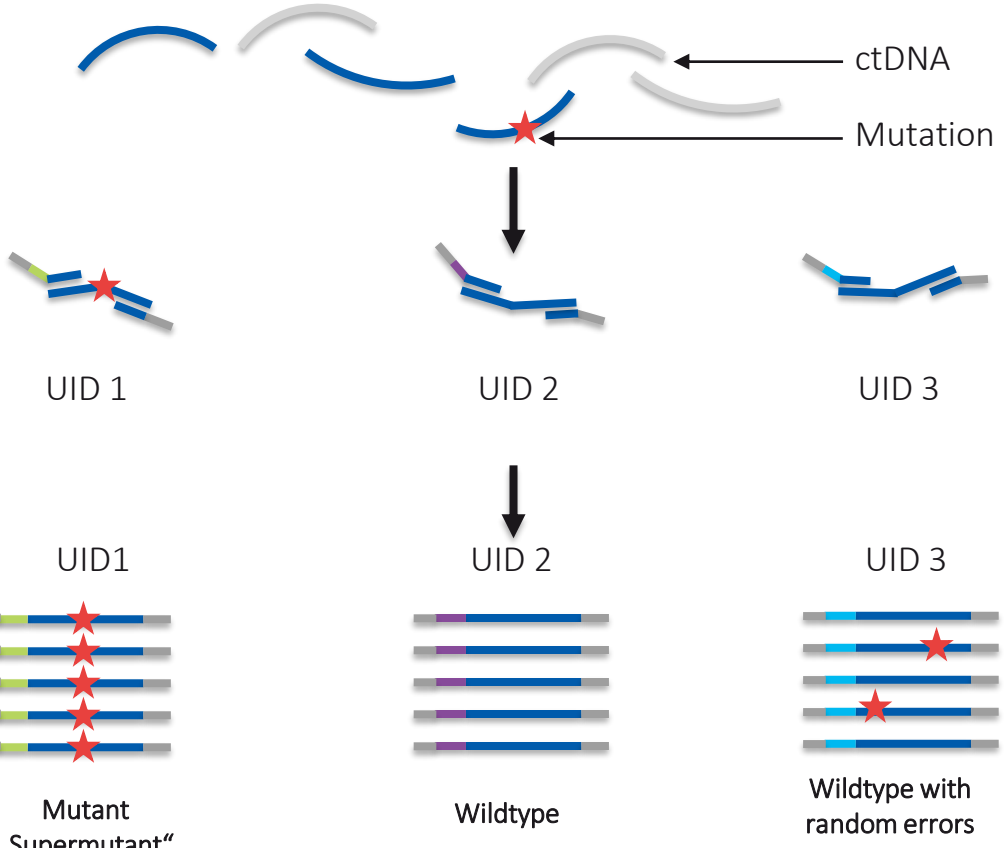



1st Day | 2nd Day

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

Kinde; et al., “Detection and quantification of rare mutations with massively parallel sequencing,” Proc Natl Acad Sci USA, vol. 108, no. 23, pp. 9530-5, 7 Jun 2011.

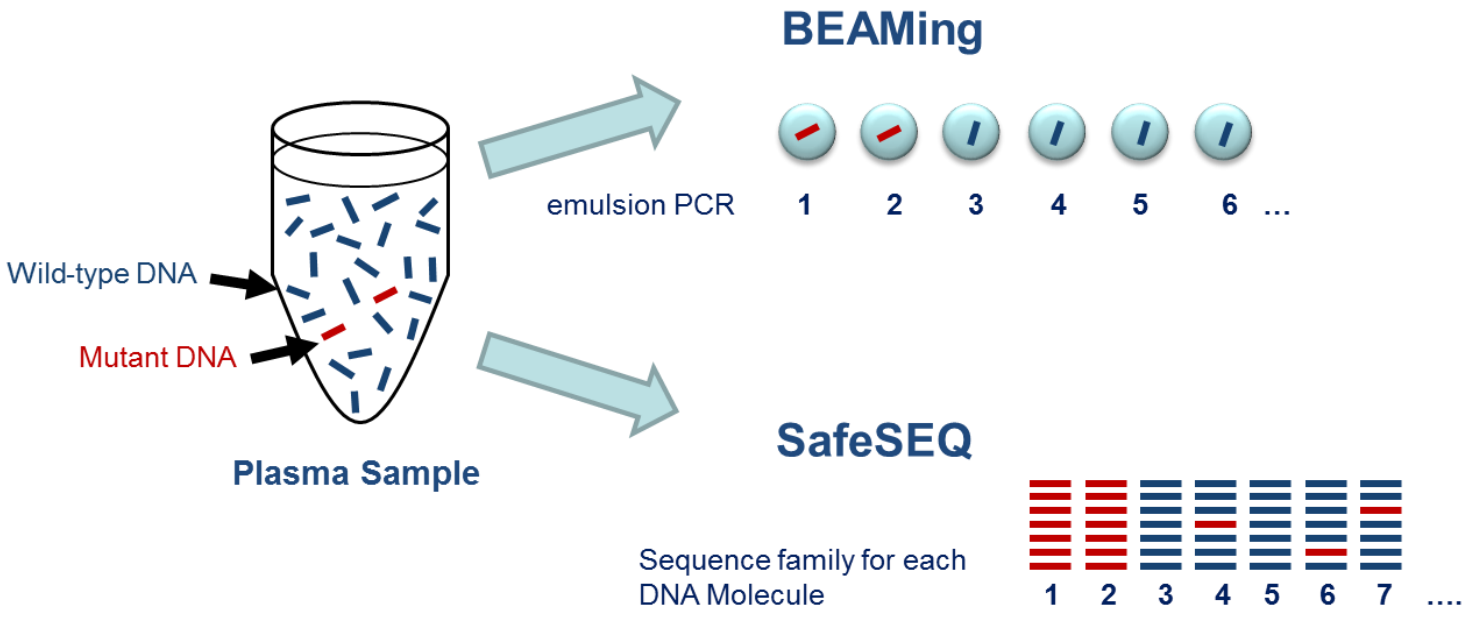
What differentiates SafeSEQ?

Designed specifically for ctDNA

Not a tissue sequencing method adapted for plasma

Amplification-based sequencing technology

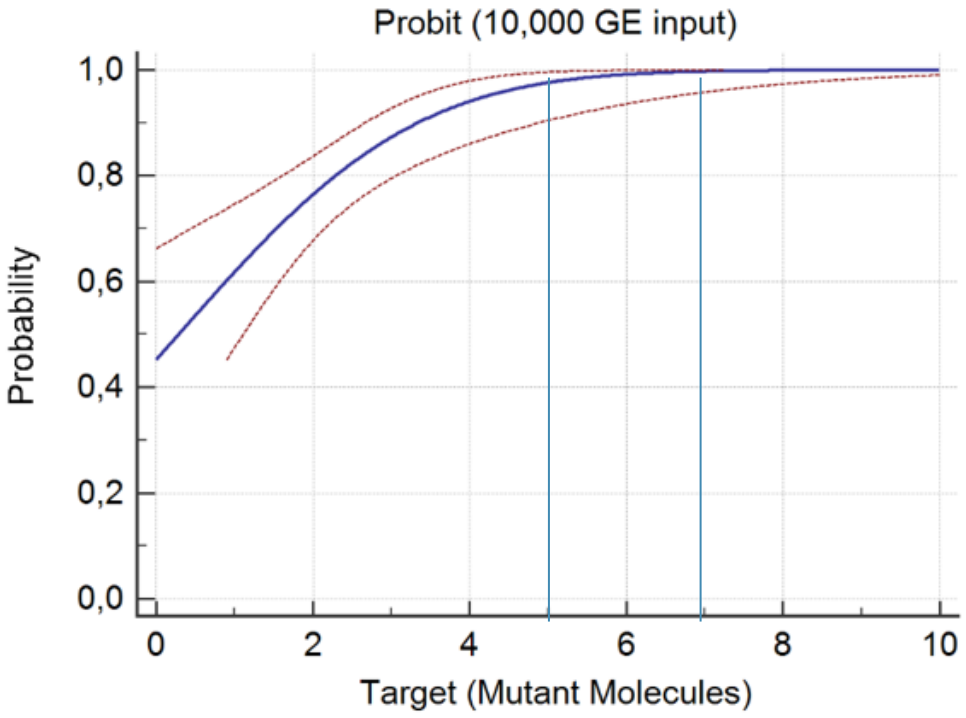
Continuing the digital approach of BEAMing

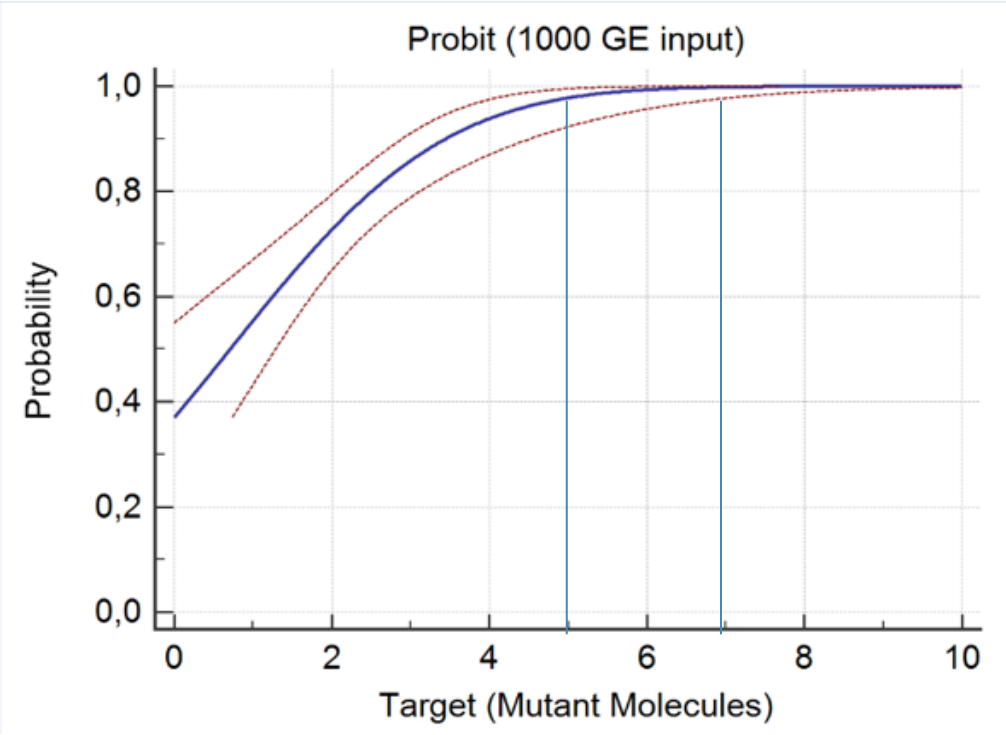


Digital analysis using molecular barcoding reduces risk of false positives

SafeSEQ demonstrates ultra-high sensitivity independent of DNA input

5-7 mutant molecules can be reliably detected

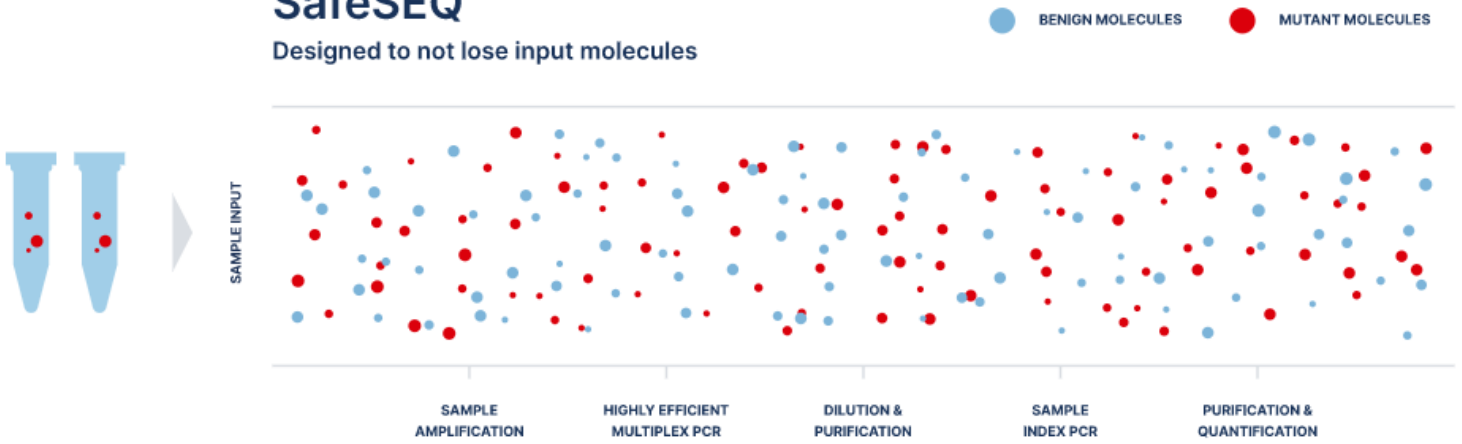




Designed to leave no molecule behind

SafeSEQ

Designed to not lose input molecules

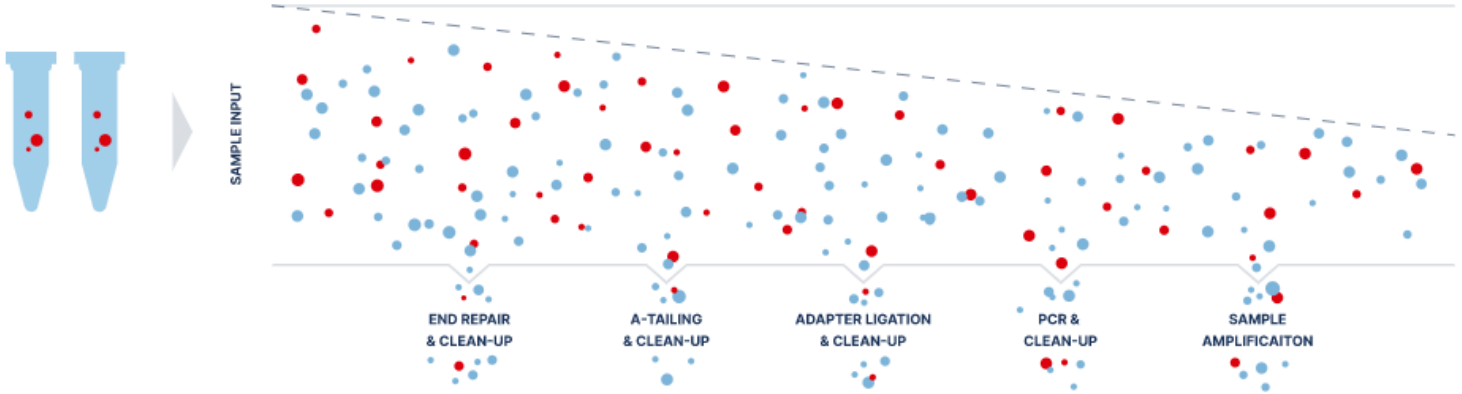


100%

of starting molecules are analyzed with SafeSEQ

Ligation/hybrid-capture based NGS

Loss of input molecules results in limited detectability

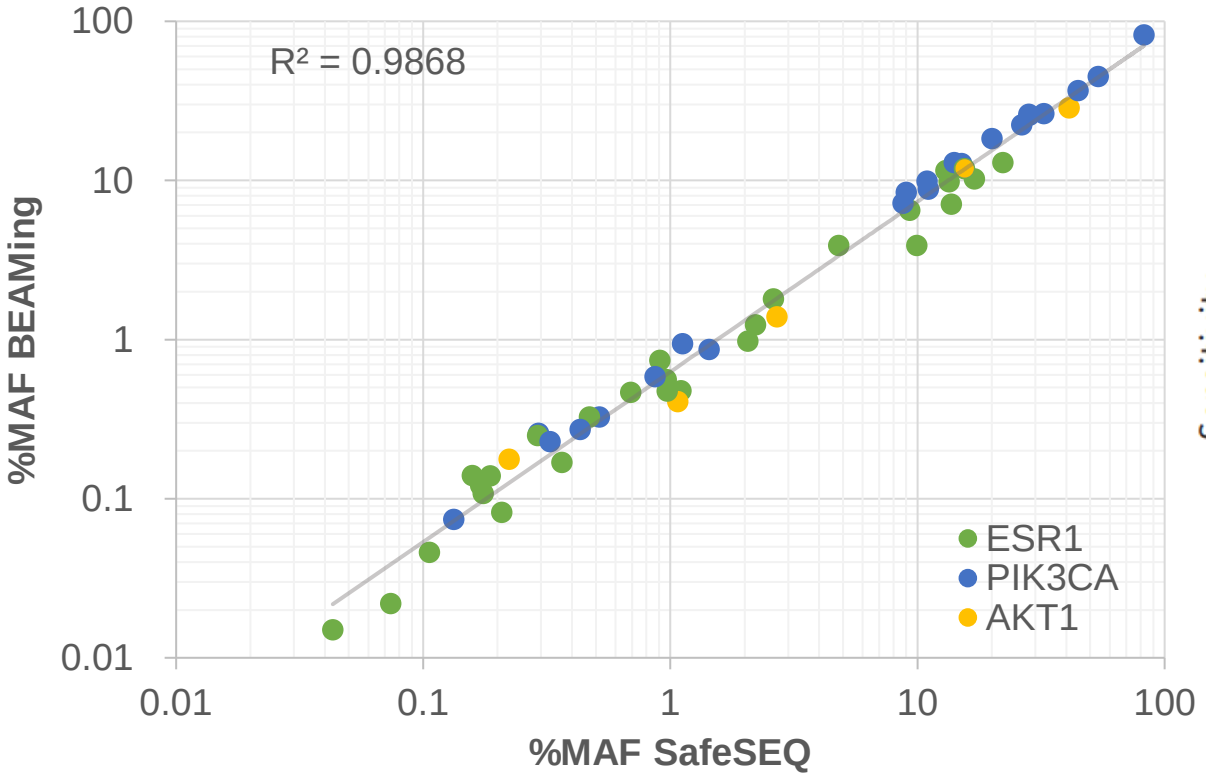


False Negative

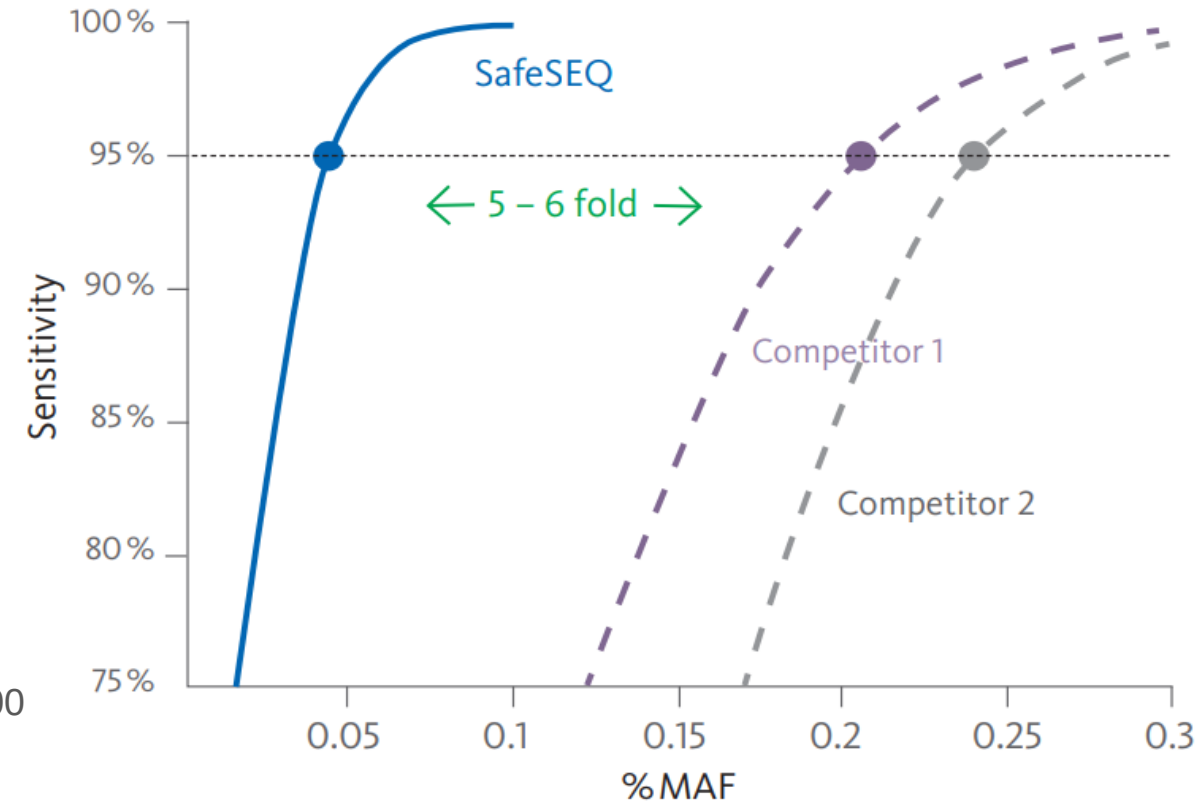
40% of molecules could be lost during sample prep prior to NGS analysis

SafeSEQ performance characterization

SafeSEQ is as sensitive as BEAMing



SafeSEQ is more sensitive than competitive assays



SafeSEQ is ideal for BioPharma

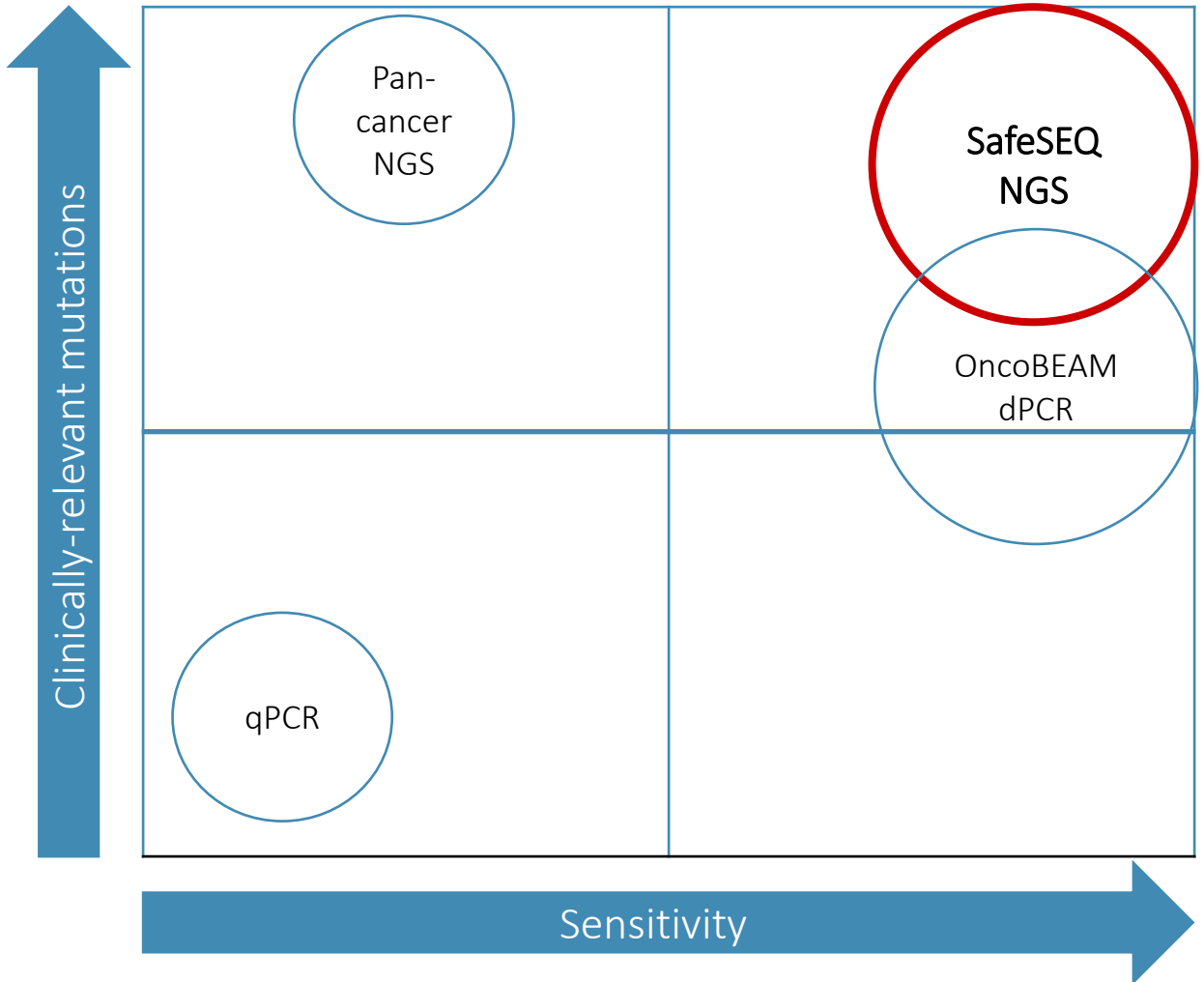
Superior therapy selection and monitoring, and MRD detection

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

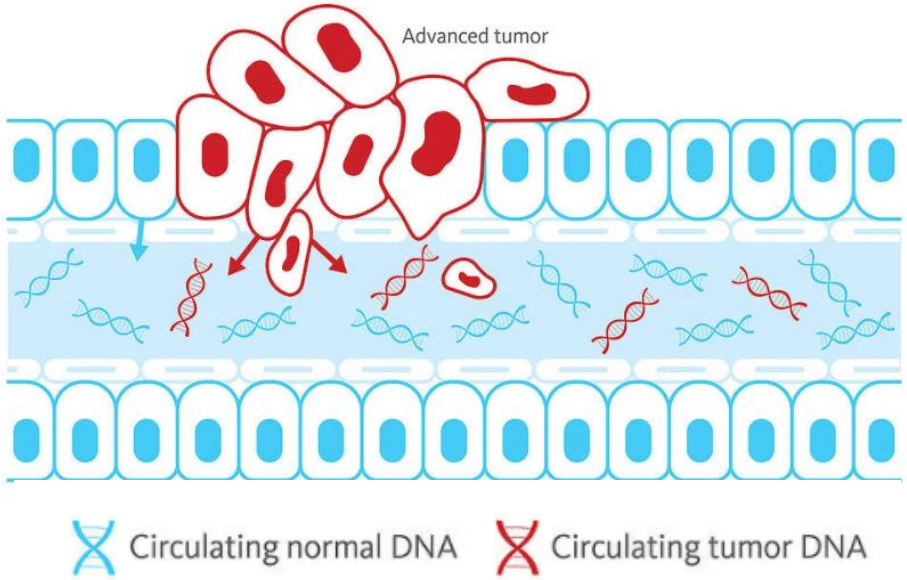
Pan-cancer NGS
- Therapy selection
- R&D biomarker discovery



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



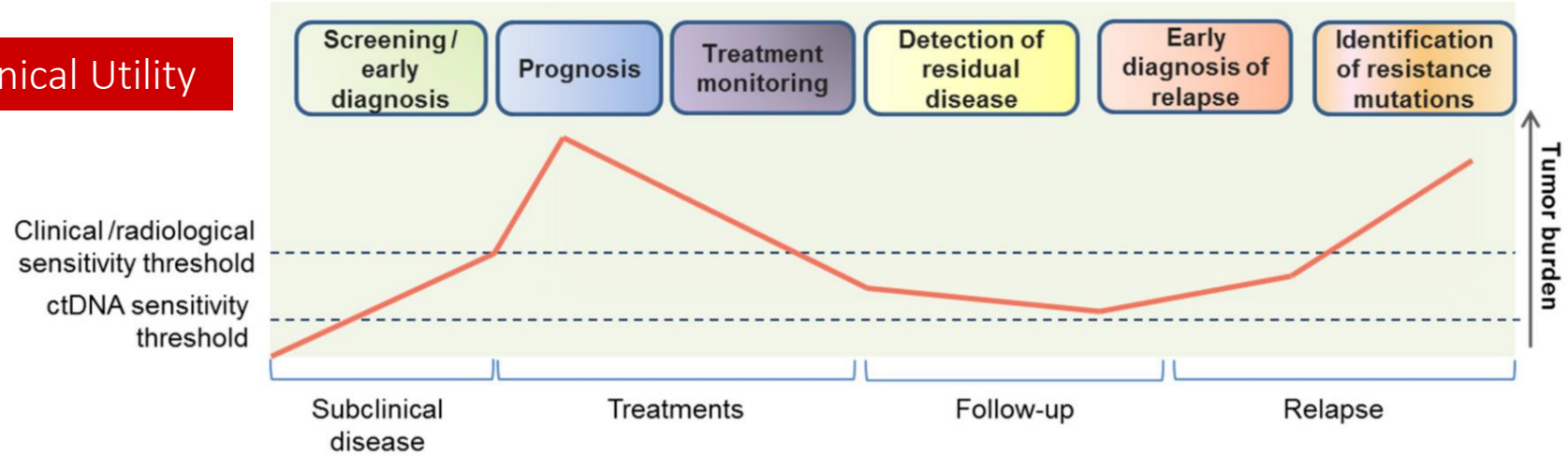
Circulating tumor DNA (ctDNA) is differentiated from circulating *normal* DNA based on the presence of somatic mutations

- 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

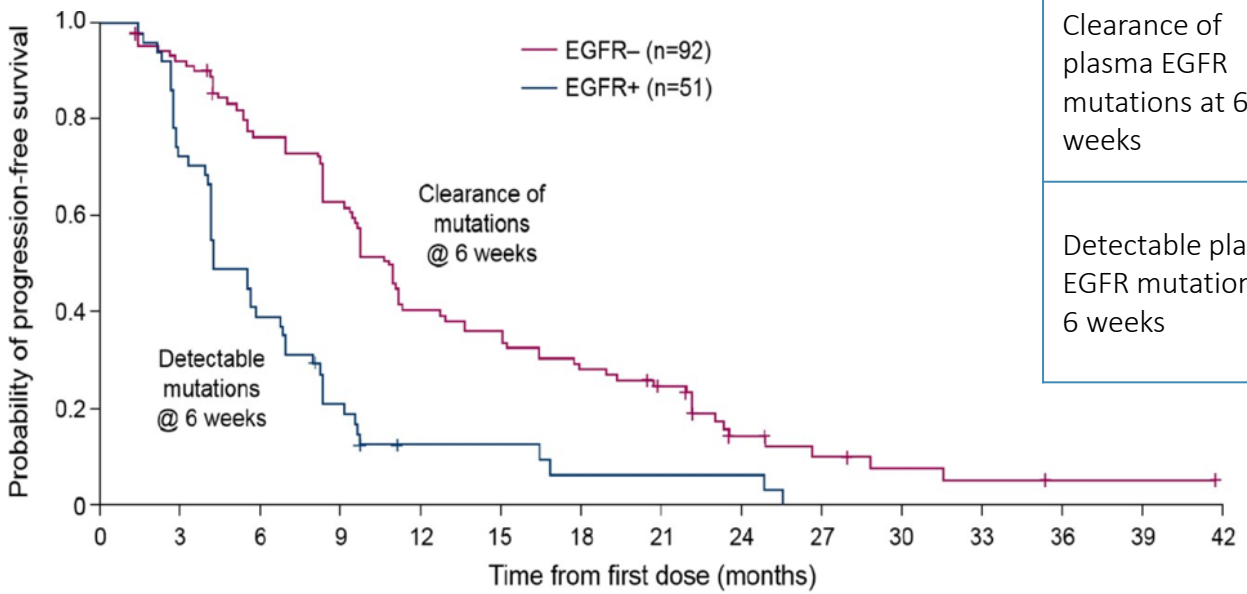
Clinical Utility



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



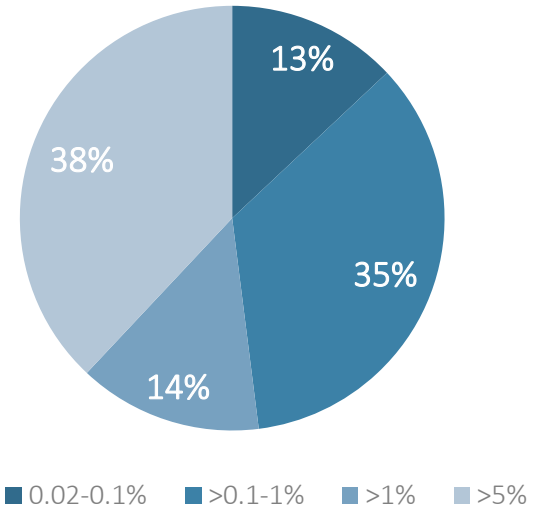
Group		Median PFS (95% CI)	ORR	P-value (log rank test)	Hazard ratio (95% CI)
Clearance of plasma EGFR mutations at 6 weeks	n=92	10.8 months 95% CI 9.3, 12.7	74%	<0.0001	2.64 (1.81, 3.84)
Detectable plasma EGFR mutations at 6 weeks	n=51	4.2 months 95% CI 4.1, 6.8	41%		

Thress, K.S., et al. Journal of Clinical Oncology 2017 35:15_suppl, 9018-9018

High sensitivity matters

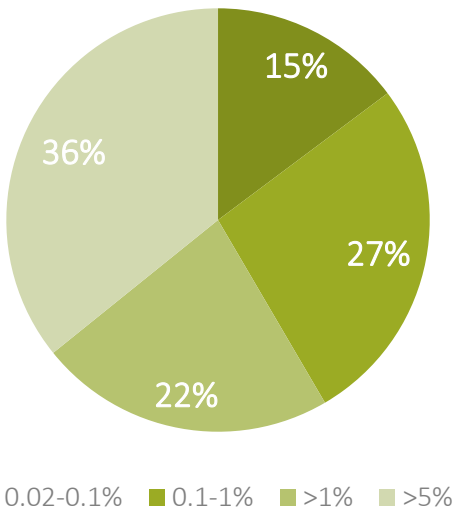
SafeSEQ and BEAMing have analytical sensitivities of ≥ 0.02-0.06%

Distribution of RAS MAFs in mCRC patients



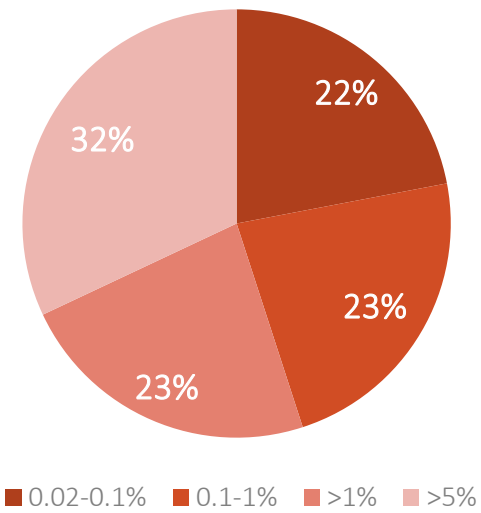
48% of patients with MAFs <1%

Distribution of EGFR MAFs in EGFR-mutant NSCLC patients with T790M+ resistance



42% of patients with MAFs <1%

Distribution of PIK3CA MAFs in HR+/HER- recurrent Breast Cancer patients



45% of patients with MAFs <1%

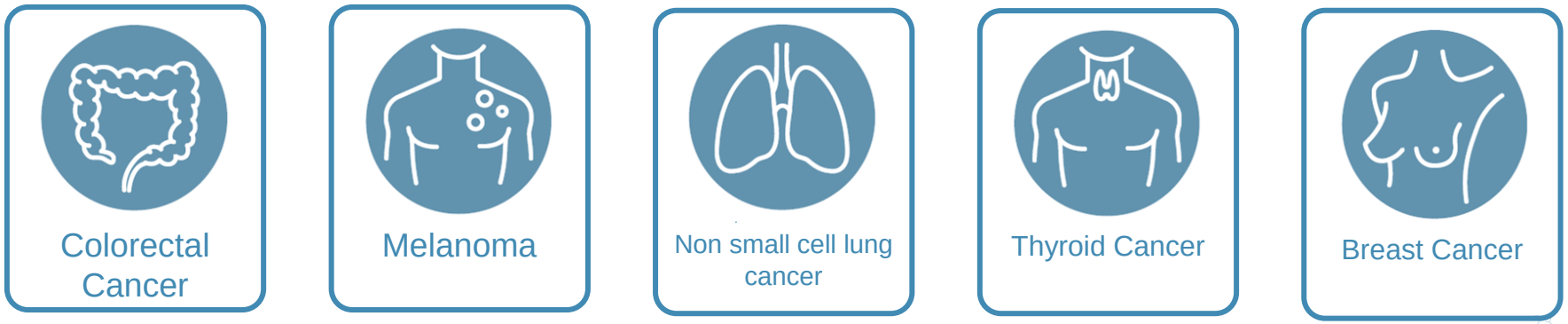
Schmiegel et al. (2017): Mol Oncol. 11(2) : 208 – 219; Saunders et al. (2016): Annals of Onc 27 (6) : 149 – 206; Vidal et al. (2017): J Clin Oncol 35 (suppl 4S; Abstract 607); Oxnard et al. (2016) J Clin Oncol 34(28):3375-3382; Baselga et al. (2015): Oral pres. SABCS, Abstract S 6 – 01

Available SafeSEQ panels

CLIA-validated panels

SafeSEQ panel	Clinically relevant gene regions	Clinical intended uses
RAS RAF pathway	AKT1, BRAF, KRAS, NRAS, PIK3CA	• Therapy selection • Therapeutic monitoring
HPV cancers	HPV 16, HPV 18	• Therapy selection • Therapeutic monitoring • Recurrence surveillance
Breast cancer	AKT1, ERBB2, ESR1, KRAS, PIK3CA, TP53	• Therapy selection • Therapeutic monitoring • Recurrence surveillance

Plasma-SeqSensei™ RUO Kit, EU ONLY

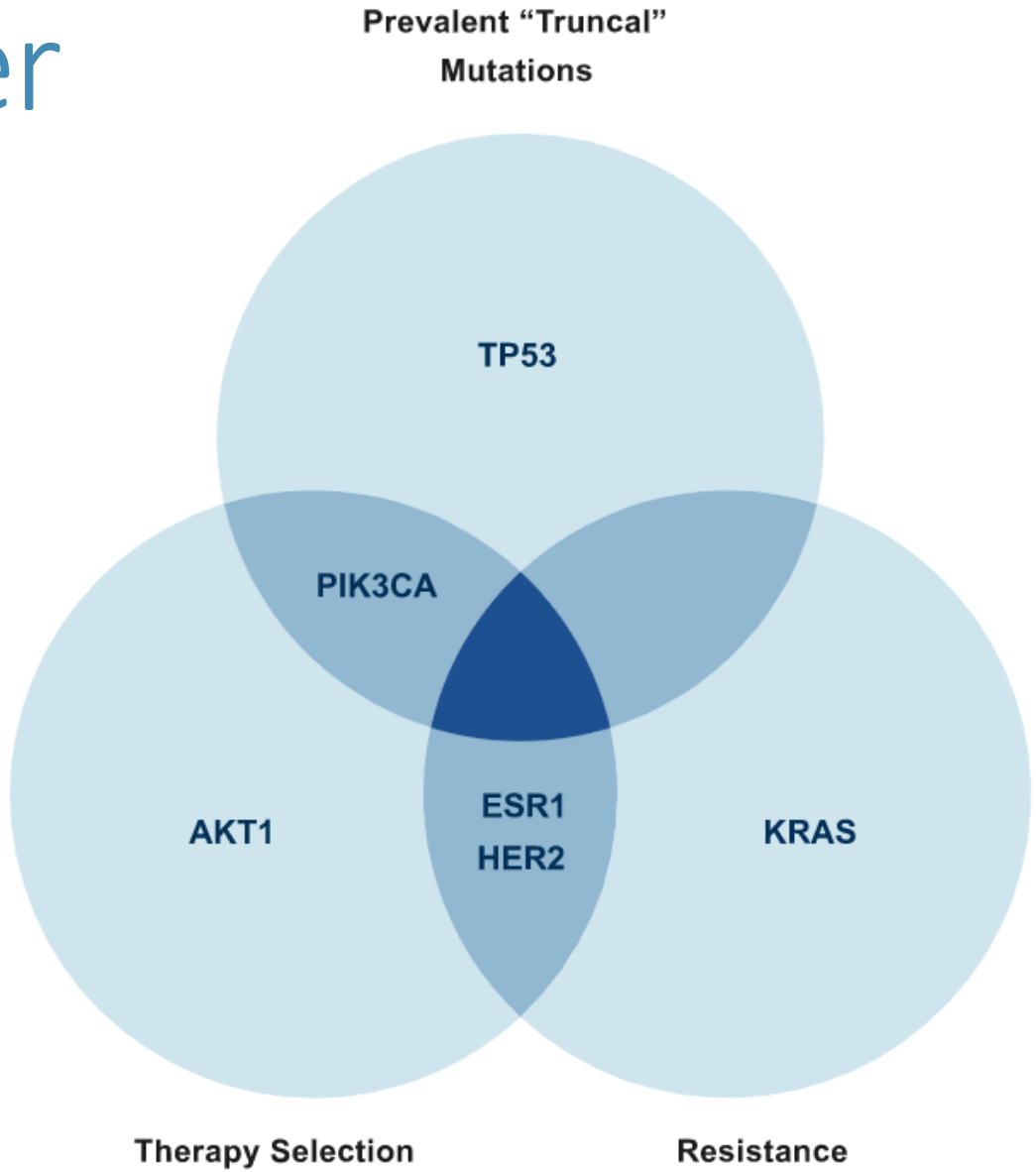


Sensitive ctDNA analysis: Clinical applications in breast cancer

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.



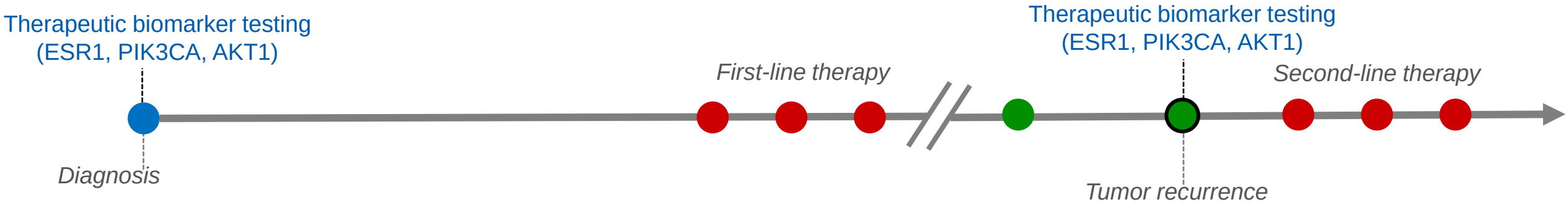
SafeSEQ BCP clinical intended uses

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**

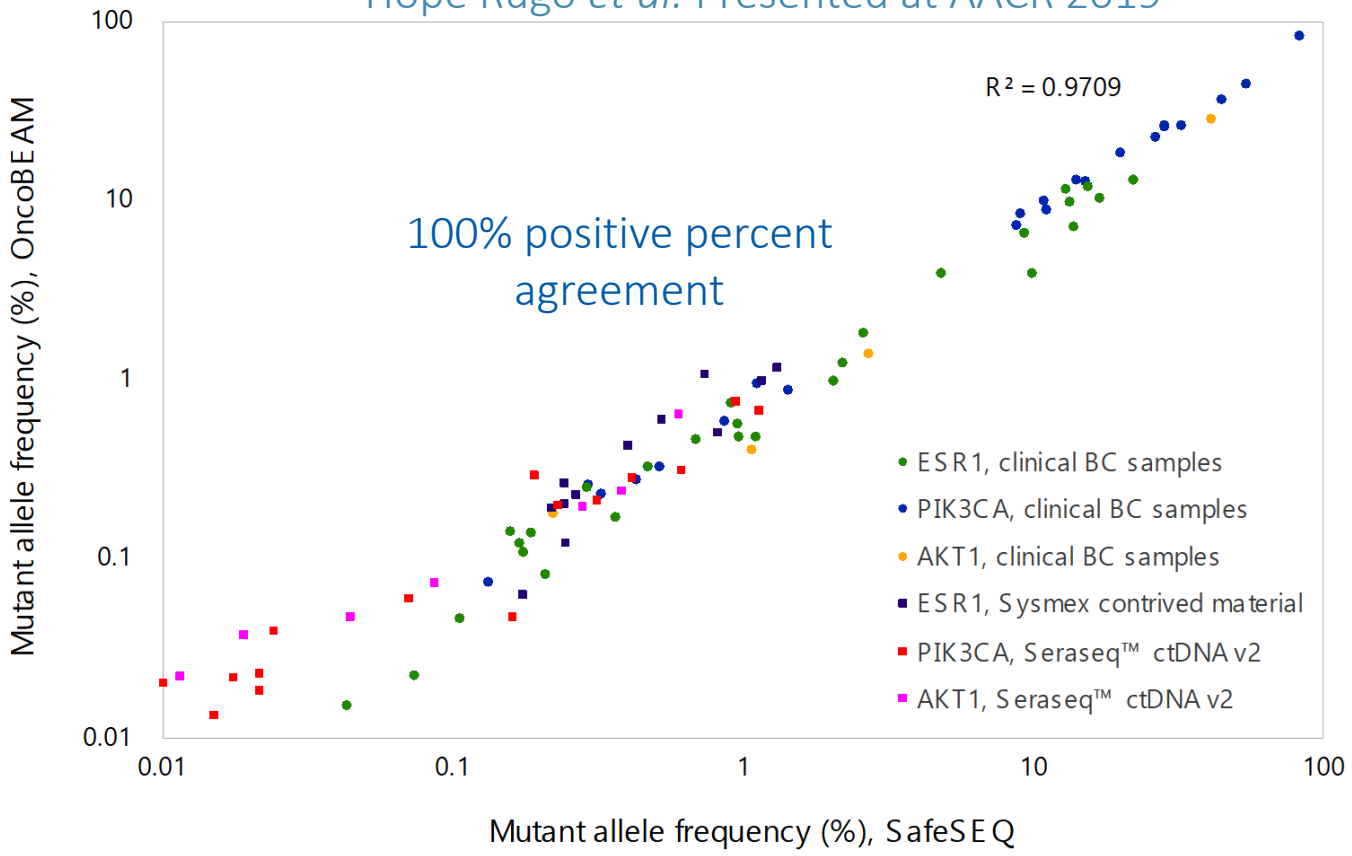


SafeSEQ has equivalent sensitivity to OncoBEAM

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)

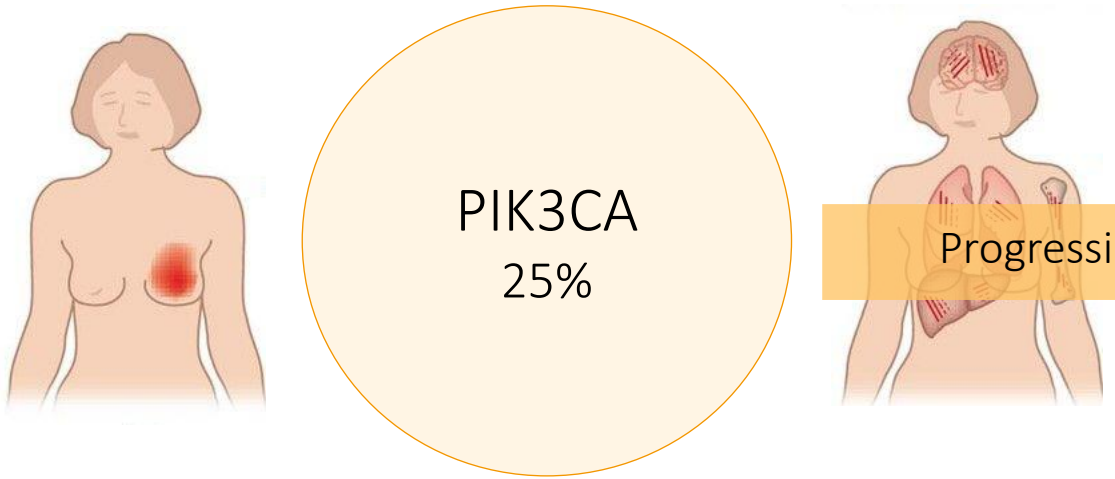
Hope Rugo *et al.* Presented at AACR 2019



ctDNA can inform treatment selection

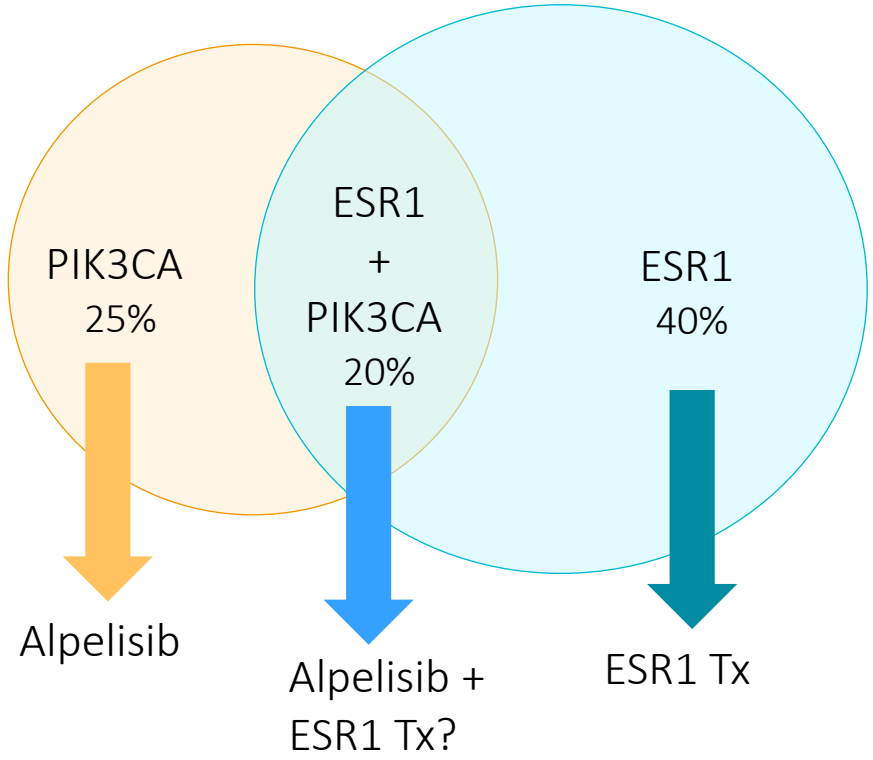
Progression and resistance monitoring

Mutation snapshot in newly diagnosed ER+/HER2- patient



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

Mutation snapshot at progression



PIK3CA testing recommended in 2nd line and will eventually include ESR1 when therapy is approved

HR(+)/HER2(-) breast cancer

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

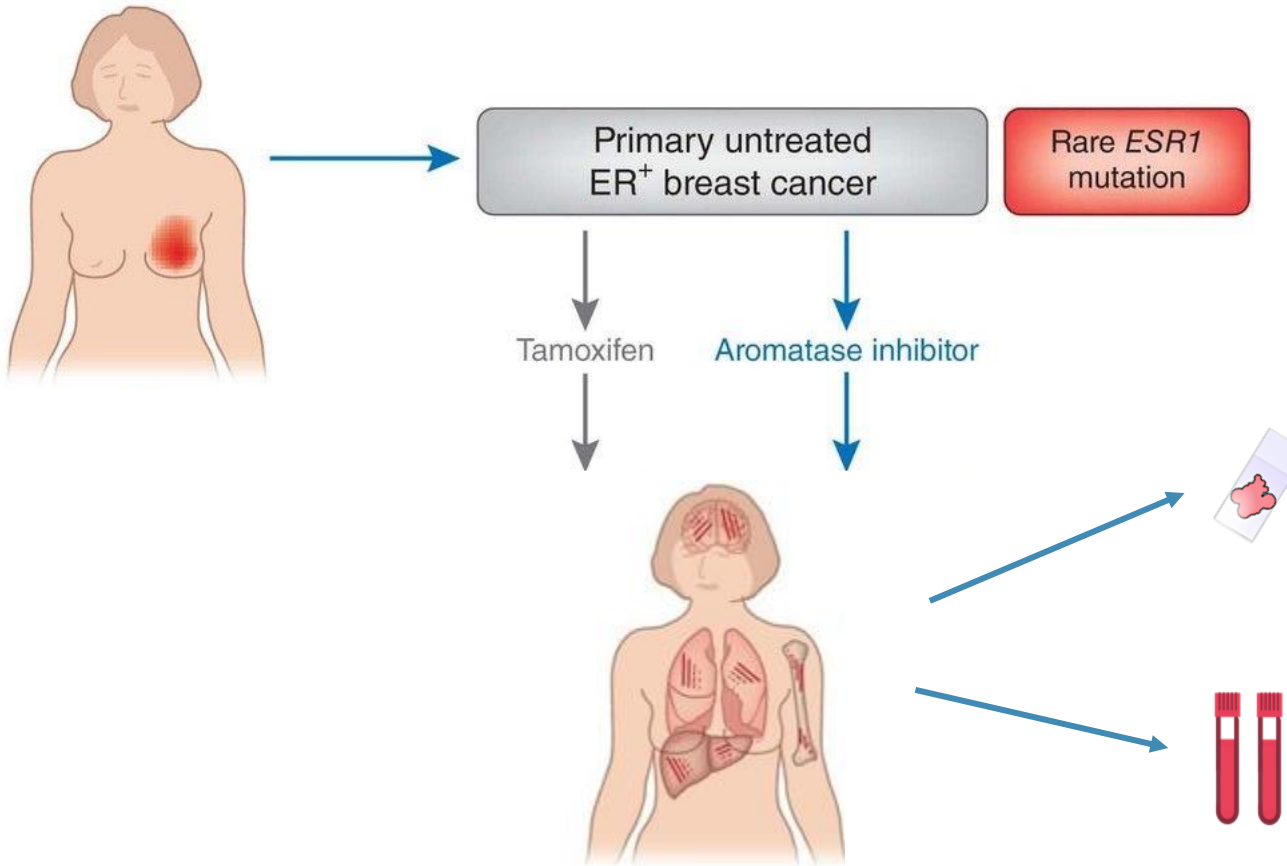
Most Commonly Mutated Genes in cfDNA

Gene	Total number of mutations found in all patients	Total number of patients with mutation	Patients with 1 mutation	Patients with >1 mutation
PIK3CA	43	27 (39%)	19	8
ESR1	40	24 (35%)	9	15
TP53*	46	30 (43%)	22	8
ERBB2	4	3 (4%)	2	1
AKT1	4	4 (6%)	4	0
KRAS*	1	1 (1.4%)	1	0

*Based on variant allele frequencies relative to other mutations, nine (9) TP53 mutations and one (1) KRAS mutation may be from clonal hematopoesis

Hope Rugo et al. Presented at AACR 2019: *Palbociclib in Combination with Fulvestrant or Tamoxifen as Treatment for Hormone Receptor-Positive (HR+) Metastatic Breast Cancer (MBC) with Prior Chemotherapy for Advanced Disease (TBCRC 035): A Phase II Study of Palbociclib Dose with Pharmacodynamics Markers*

ESR1 mutation detection is essential for drugs targeting ER+/HER2- patients in clinical trials



Tissue testing for ESR1 not suitable due to molecular heterogeneity

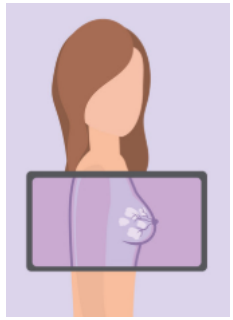
Blood-based testing maximizes identification of patients

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)

5 years? >5 years?

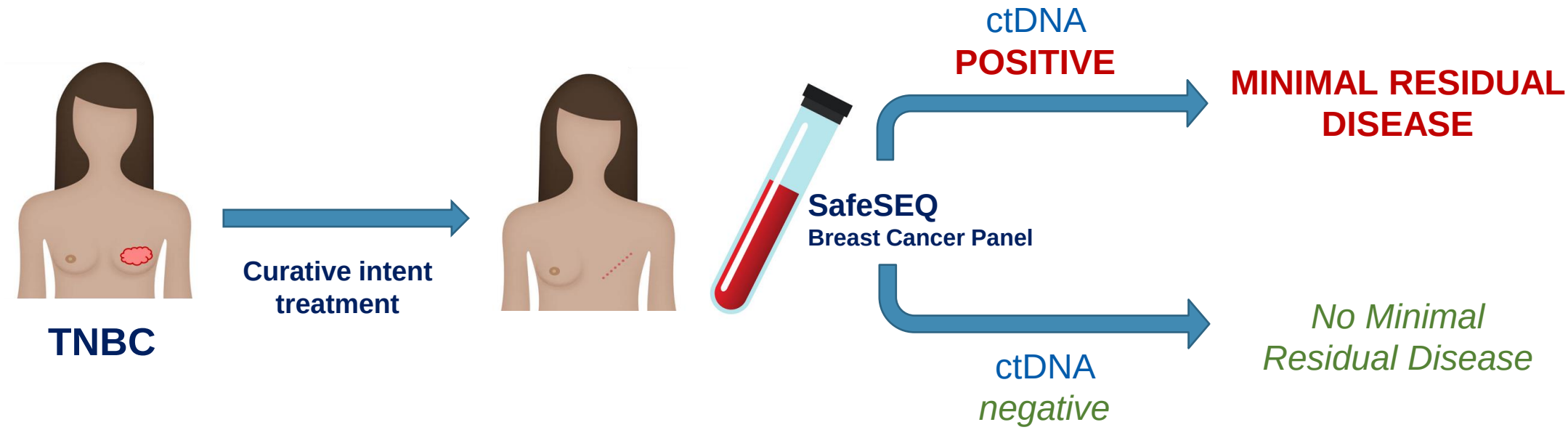
Hormone therapy (± chemotherapy)

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



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:

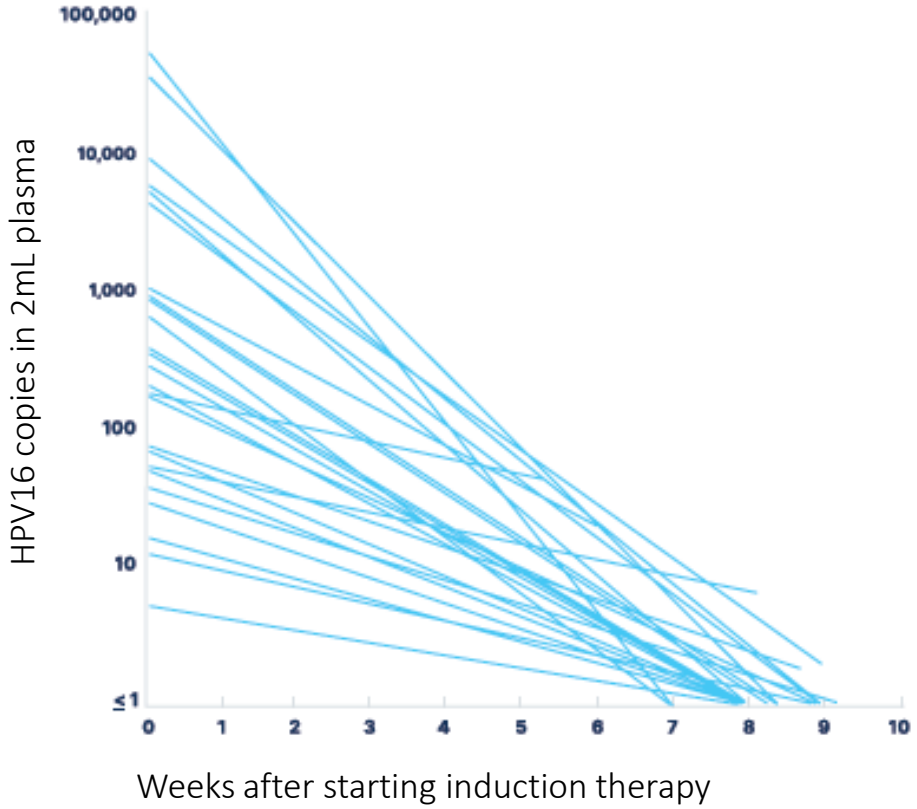
Sensitive detection of HPV 16 and HPV 18 in plasma across a broad dynamic range (over 5 orders of magnitude).

- 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

Sloane, H. et al. (2021) 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. J Clin Oncol. 39:15_suppl, 6048.

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.

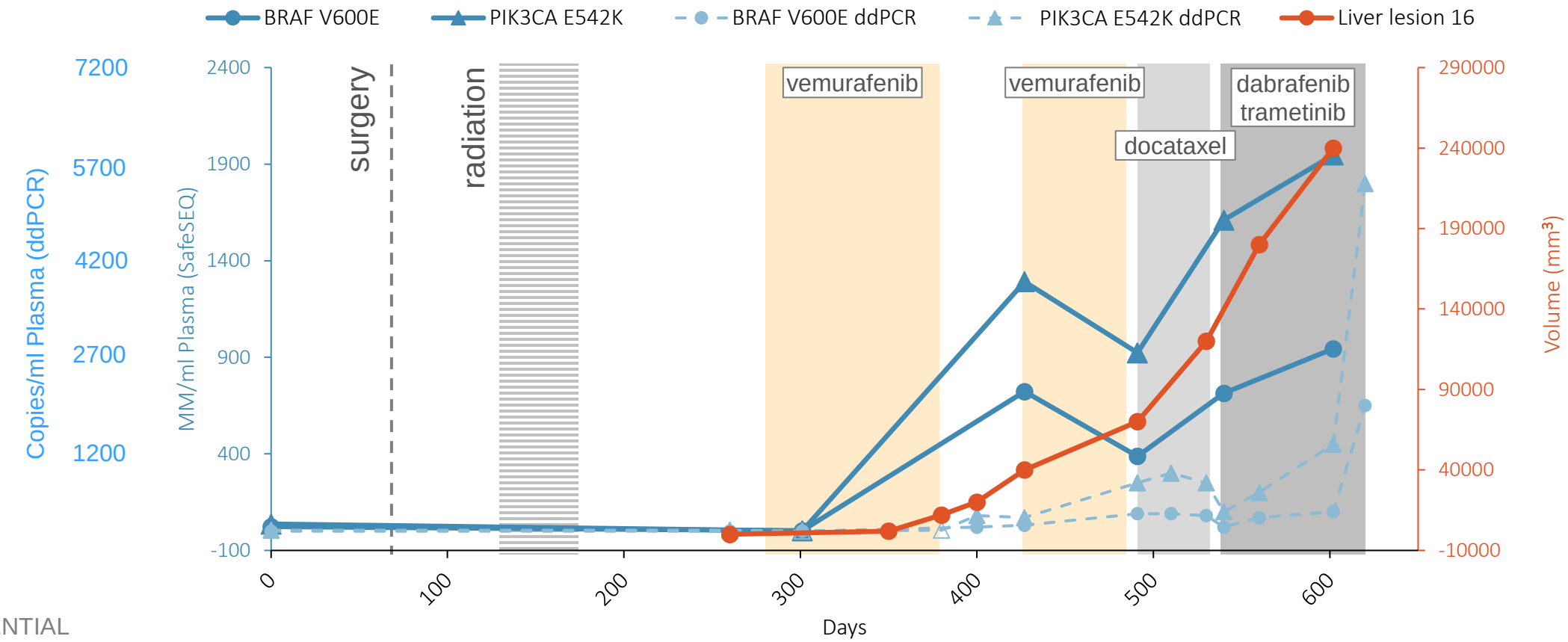
Allow for individualized decisions to optimally refine treatment strategies.

Serve as useful intermediate endpoints and improve efficiency of clinical trials.

Clinical cases showing value of SafeSEQ ctDNA detection

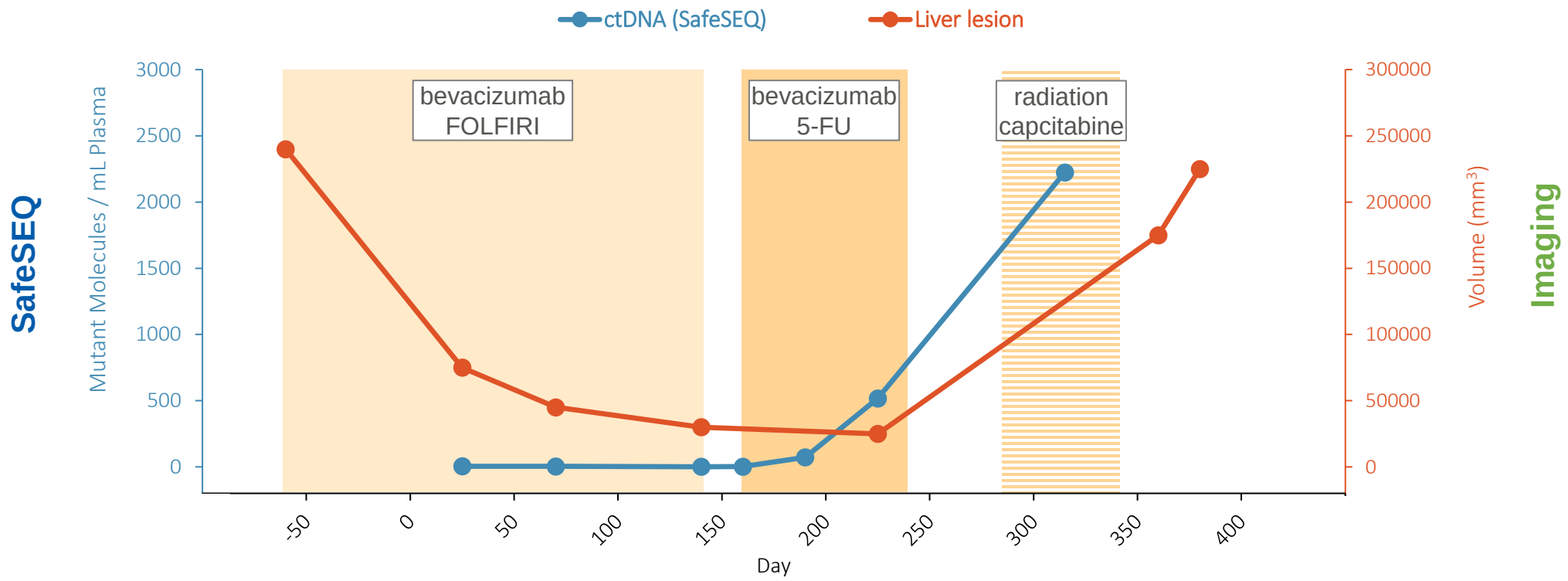
Case study 1: BRAF-targeted therapy monitoring in NSCLC

- 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

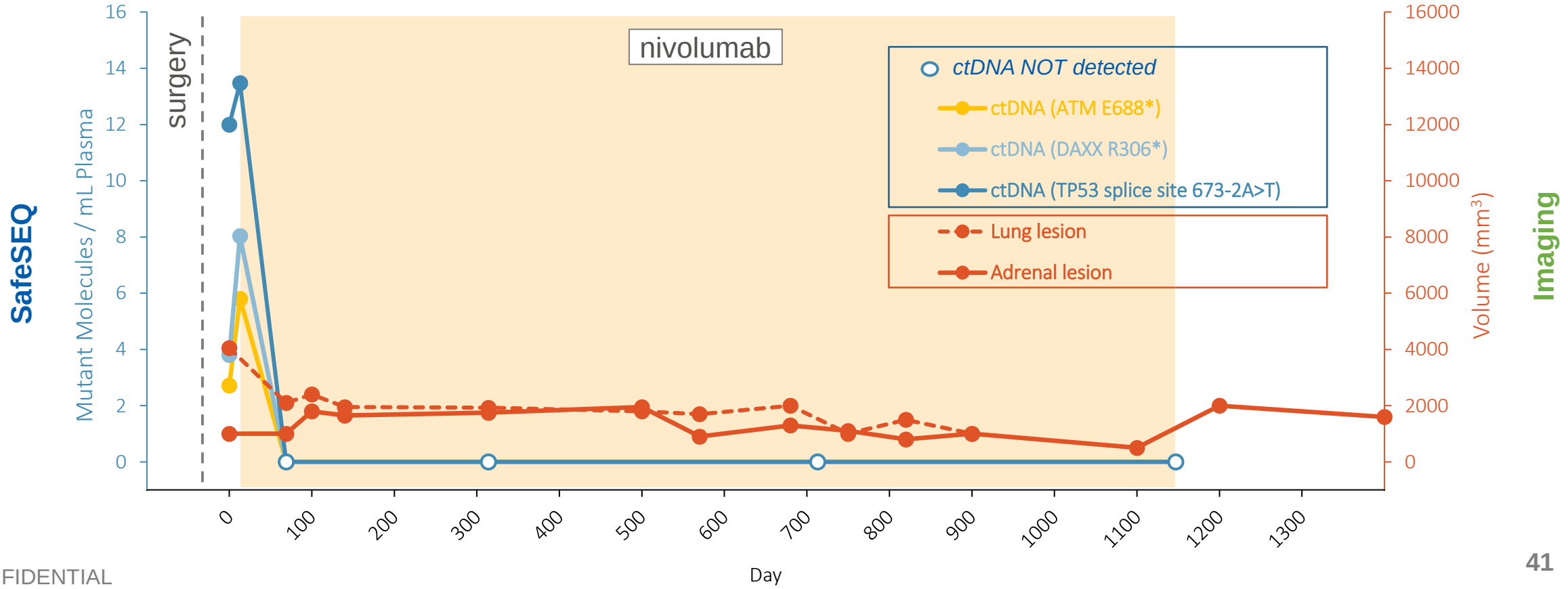
- **Goal:** Assess feasibility of ctDNA as an indicator of tumor burden in patients with advanced solid tumors treated with immunotherapy.

- **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:

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Q&A