The need of metrological traceability in cancer molecular diagnostics.

- Set-Up/Validation/Verification of a DPYD Genotyping workflow
- The need for metrological traceability in liquid biopsy

About Us

At a glance

- SensID GmbH was established in Dec 2015
  - 1st product to market Nov 2018
- Rostock (Germany) site with 3 areas:
  - Production
  - Quality Assurance
  - Research and Development
- Currently:
  - > 50 off the shelf products
  - X number of custom products

Management System EN ISO 13485:2016
TÜVRheinland CERTIFIED
www.tuv.com ID 9000009213

- Ambition: Unlimited!

Founding team & Management

Björn Nowack
Managing Director, R&D
Dipl.-Biochemist

Andreas Bollmann
Production, QM
Dipl.-Ing. Biotechnologist (FH)

Sven Rüger
Finances, Human Ressources
Dipl.-Economist (FH)

Our Philosophy

Vision

Become the leading
ISO 17034 accredited company
focused on clinical genomics with the
major aim to support our customers
in
meeting regulatory and quality
requirements

Mission

Provide customized standards on
demand and in time that are a true
fit to your needs in
assay & instrument development,
validation and implementation

Values

Being a true partner for you and all
your projects and work with full
openness and honesty at every
aspect of a
real partnership

Where are reference materials used?

Pre-analytical Evaluation

- Sample Matrix
- Collection/Collection tubes
- Transport
- Processing
- Storage / Repeated use (freeze / thaw cycles)
- Extraction Procedures
- Quality/Quantity of examination material

Analytical Evaluation

- Accuracy / Precision
- Repeatability / Reproducibility
- Analytical specificity / sensitivity
- LOD / LOQ / LOB
- Linearity
- Interference
- Robustness / controls

Assay Performance Issues

- EQA schemes
- Customer presentation controls
- Batch release controls
- Daily run controls in diagnostic procedure
- In kit controls
- …

Available products – Overview

Different categories made for different purposes

gDNA & cfDNA in Buffer

gDNA
Heriditary diseases
PGx
NIPT (Rhesus factor)

cfDNA/ctDNA
Liquid Biopsy
Breast/Colon/
Lung/…

cfDNA & Plasma

Plasma
+ cfDNA/ctDNA
Liquid Biopsy
Extraction efficiency
Full workflow control

Certified DNA free
human Plasma
Make your own Plasma
control
NEW: Exosome free!

FFPE Tissue

FFPE
Blocks/Slices/Cells
Extraction efficiency
Full workflow control

Development Pipeline
methylated DNA
WES-Reference Material
WGS-Reference Material
NIPT/NIPD

Development Pipeline
RNA
Nucleosomes
methylated DNA
Infectious disease

Development Pipeline
MSI/MSS
Multiplex Panels
RNA (Fusions)
CTCs

Exclusive Development throughout the Product Range

Targeted approach, custom made controls

Our products come:

In different categories

- gDNA, cfDNA/ctDNA, Plasma + cfDNA/ctDNA, FFPE

Via different technologies

- Cell lines (SensID proprietary with family background, or in licensed), synthetically designed variants, technically modified human plasma, combinations

In regulatory and customer compliance

- CE-IVD (incl. technical documentation) or RUO
- OEM & licensing options

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ID 9000009213

Including customization of

- Allelic frequencies, mutant copies, DNA concentration
- Filling volumes, vial, labels to exact specifications
- And much more…

www.sens-id.com

1st example:
Liquid biopsy, the frontiers of technology?

Cancer Manag Res. 2019; 11: 5271–5291. PMCID: PMC6559244
Published online 2019 Jun 6. doi: 10.2147/CMAR.S170380 PMID: 31239778

Current status of liquid biopsies for the detection and management of prostate cancer

Yi-Tsung Lu,[1] Kevin Delijani,[1] Andrew Mecum,[1] and Amir Goldkorn[1]

In a recent report, more than 10,000 samples were tested by the assay, and the authors reported a detection limit of 0.02% of allelic fraction

LIQUID BIOPSIES
(circulating tumour cells, circulating nucleic acids, exosomes)

ADVANTAGES	CLINICAL APPLICATIONS	LIMITATIONS
• Isolation from many biological fluids and sources of non-invasive biomarkers	• Screening for cancers in high-risk populations	• Molecular protocols need to be standardized: still too few laboratory applications
• Less expensive, quick and easily	• Early diagnosis of cancer and monitoring early therapeutic response	• Management of small amounts

FDA approves liquid biopsy NGS companion diagnostic test for multiple cancers and biomarkers

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ctober 26 and November 6, 2020, the Food and Drug Administration approved the biopsy next-generation sequencing-based FoundationOne Liquid CDx test dation Medicine, Inc.) as a companion diagnostic device for multiple additional arkers detected in cell free-DNA isolated from plasma specimens.

ompanion diagnostic indications in the October 26 approval are 1) to identify ions in *BRCA1* and *BRCA2* genes in patients with ovarian cancer eligible for nent with rucaparib (RUBRACA, Clovis Oncology, Inc.), 2) to identify *ALK* angements in patients with non-small cell lung cancer (NSCLC) eligible for treatment lectinib (ALECENSA, Genentech USA, Inc). and 3) to identify mutations in the *CA* gene in patients with breast cancer eligible for treatment with alpelisib (PIQRAY, rtis Pharmaceutical Corporation).

ovember 6, FDA approved the FoundationOne Liquid CDx test as a companion ostic device to identify mutations in *BRCA1*, *BRCA2* and *ATM* genes in patients with static castration resistance prostate cancer (mCRPC) eligible for treatment with rib (LYNPARZA, AstraZeneca Pharmaceuticals LP).

dationOne Liquid CDx approval as a companion diagnostic for rucaparib, alpelisib, nib, and olaparib was based on the retrospective testing with FoundationOne Liquid f available plasma samples from patients enrolled in four clinical trials that

FDA-Led Group Evaluates Performance of RUO Liquid Biopsy Assays to Inform Practice Guidelines

Apr 13, 2021 | John Gilmore

Premium

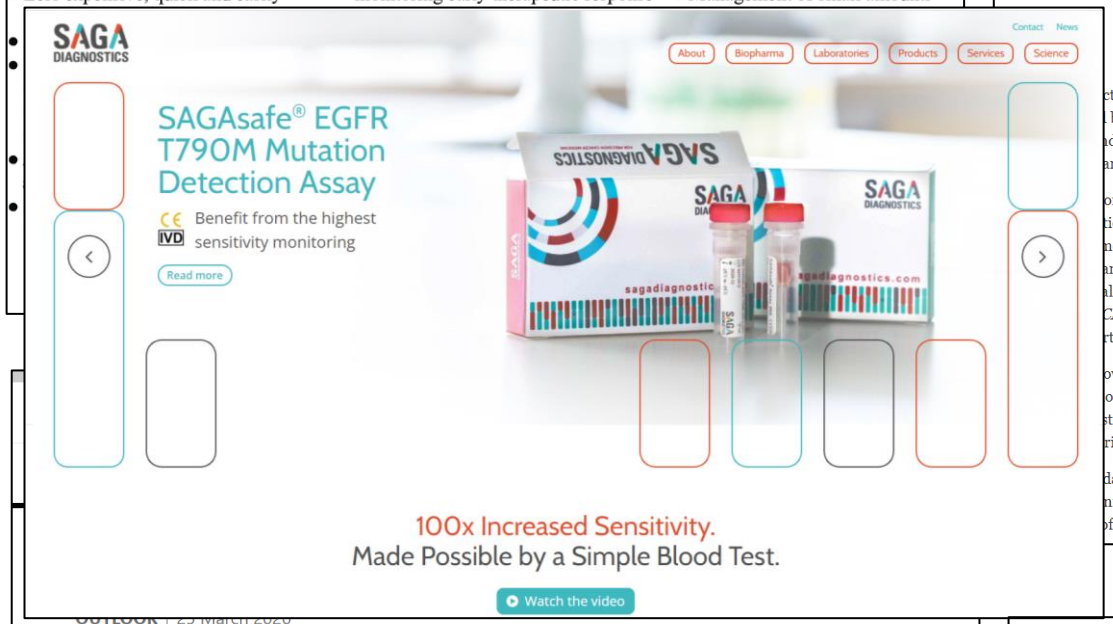
NEW YORK – A consortium led by US Food and Drug Administration investigators has evaluated the analytical performance of five research-use-only liquid biopsy next-generation sequencing (NGS) assays for different clinical applications and to help inform practice guidelines for the precision oncology space.

The team also saw that the reliable sampling of rare circulating tumor DNA fragments served as the major challenge for developing novel liquid biopsy assays.

Joshua Xu, a computer scientist in the FDA's division of bioinformatics and biostatistics, explained that his team launched a project in 2016 called Sequencing Quality Control Phase 2 (SEQC2) to develop standard analysis protocols and quality control metrics for the use of NGS data to enhance regulatory science research and precision medicine.

The FDA has currently approved two ctDNA-based liquid biopsy tests that have high sensitivities for allele frequencies (AF) of about 0.3 percent, Foundation Medicine's FoundationOne Liquid CDx and Guardant Health's next-generation sequencing (NGS) Guardant360 CDx pan-cancer assay.

Xu said that manufacturers of the RUO sequencing kits have published studies that claim to reach lower allele frequencies — even as far down as 0.01 percent — than currently approved assays. However, he noted that reports exist that also claim there is a lack of concordance between what manufacturers claim and the performance that clinical labs see.



OUTLOOK | 29 March 2023

Could liquid biopsies help deliver better treatment?

Tests that capture tumour signatures in the blood have the potential to detect cancer before symptoms appear.

The SAGAsafe® technology is based on droplet digital PCR and can reliably detect and quantify mutations to ~0.001% mutant allele frequency (MAF), the new standard of *ultrasensitivity*.

What does the EU regulation say?

- According to the regulation (EU) 2017/246 (IVDR), IVDs must include metrologically traceable controls and measurement methods to ensure the performance of an IVD.

Chapter II - REQUIREMENTS REGARDING PERFORMANCE, DESIGN AND MANUFACTURE

- 9.3. Where the performance of devices depends on the use of calibrators and/or control materials, the metrological traceability of values assigned to calibrators and/or control materials shall be assured through suitable reference measurement procedures and/or suitable reference materials of a higher metrological order. Where available, metrological traceability of values assigned to calibrators and control materials shall be assured to certified reference materials or reference measurement procedures.

ANNEX XIII

PERFORMANCE EVALUATION, PERFORMANCE STUDIES AND POST-MARKET PERFORMANCE FOLLOW-UP

PART A - PERFORMANCE EVALUATION AND PERFORMANCE STUDIES

1.1. Performance evaluation plan

- identification of certified reference materials or reference measurement procedures to allow for metrological traceability;

1:Link
2: Link to CPIC guideline

1st example:
Liquid biopsy, the frontiers of technology?

genomeweb

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Home » Disease Areas » Cancer

Saga Diagnostics, SensID to Codevelop Control Reagents for Cancer Mutation Detection

Jul 17, 2020 | staff reporter

NEW YORK –Swedish personalized cancer genomics startup Saga Diagnostics and Rostock, Germany-based SensID said on Wednesday that they have partnered to develop control reagents for cancer mutation detection.

The European collaborators will use SensID's controls with Saga's digital PCR-based Sagasafe technology, which can detect and quantify circulating tumor DNA in cancer patients at ultra-low allelic frequencies (AF).

SensID develops, manufactures, and markets quality controls and reference materials for clinical genomics and DNA diagnostics.

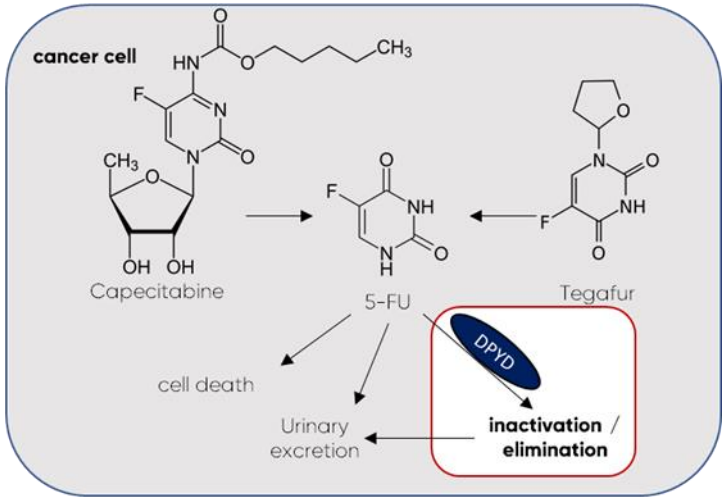
"Developing and manufacturing controls can only be done accurately and [reproducibly] if the [quality control] methods 100 percent fit the finalized product," Bjoern Nowack, CEO and cofounder of SensID, said in a statement. "With the AF going down to the demand of Saga, we need a different technology to run our [quality control] the way it should be run."

Financial details of the agreement were not disclosed.

"In order to speed up the ability of our customers to verify our ultrasensitive mutation detection kits and services, we require reliable third-party reference controls that go well below 0.1 percent AFs," Lao Saal, CEO and cofounder of Lund-based Saga Diagnostics, added.

Need of metrological traceability in cancer diagnostics- 2nd example: DPYD genotyping

- 5-Fluorouracil (5-FU) and capecitabine (CAP) are among the most frequently prescribed anticancer drugs (chemotherapy)
- 5-Fluorouracil (5-FU) is degraded by dihyropyrimidine dehydrogenase (DPYD)



Need of metrological traceability in cancer diagnostics- 2nd example: DPYD genotyping

The review (on DPYD)was initiated March 2019 at the request of the French Medicines Agency (ANSM), under Article 31 of Directive 2001/83/EC.

NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
E-mail: ReferralNotifications@ema.europa.eu

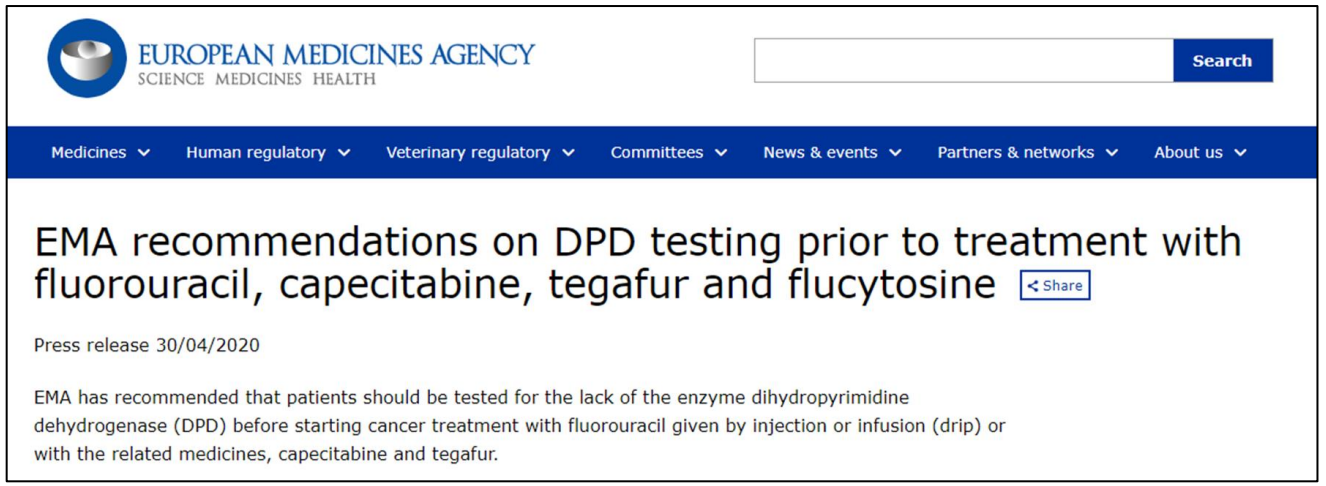
This notification is a referral under Article 31 of Directive 2001/83/EC to the PRAC made by France (ANSM):

Product names in the referring member states	XELODA capecitabine-containing medicinal products 5-fluorouracil-containing medicinal products (i.v. application) TEYSUNO Tegafur containing medicinal products
Active substances	Capecitabine 5-fluorouracil Tegafur

https://www.sens-id.com/shop/gdna-en/sid-000110/

Text from the review

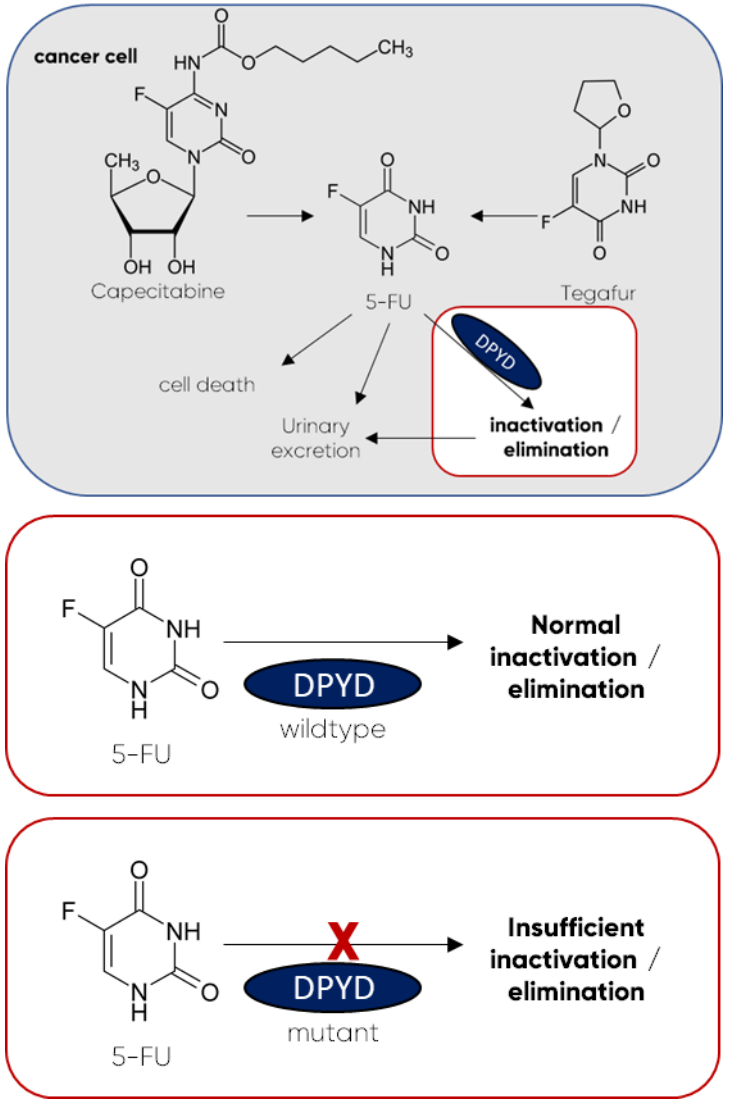
In the Caucasian population, approximately 3-5% has a partial DPD deficiency and 0.01-0.5% is fully DPD deficient. The estimate prevalence of patient experiencing a serious toxicity is between 15-30%, and the estimate prevalence of patient experiencing a lethal toxicity potentially due to DPD deficiency is around 2%(1). In France, with about 80 000 patients exposed to capecitabine or 5-FU yearly, the number of toxic deaths (whatever the origin of the death) is thus estimated to be about 1600, and the number of serious toxicity between 12.000 and 24.000. It is acknowledged that as the detection of DPD deficiency is not done routinely, it is not possible to calculate the exact number of cases exclusively related to DPD deficiency.



https://www.sens-id.com/shop/gdna-en/sid-000110/

Need of metrological traceability in cancer diagnostics- 1st example: DPYD genotyping

- 5-Fluorouracil (5-FU) and capecitabine (CAP) are among the most frequently prescribed anticancer drugs
- 5-Fluorouracil (5-FU) is degraded by dihyropyrimidine dehydrogenase (DPYD)
- Around 3% of the population is DPD deficient and these patients have a significantly increased risk of severe and potentially lethal toxicity when treated with regular doses of 5-FU or CAP
- Various national guidelines for colon carcinoma were updated to recommend DPYD genotyping before treatment with 5-FU or CAP (EMA recommendation)
- Mutations are found heterozygous as well as homozygous and that has influence on therapeutic decision so determination of exact AF is needed



Need of metrological traceability in cancer diagnostics- 1st example: DPYD genotyping

- Around 3% of the population is DPD deficient and these patients have a significantly increased risk of severe and potentially lethal toxicity when treated with regular doses of 5-FU or CAP
- Mutations are found heterozygous as well as homozygous and that has influence on therapeutic decision so determination of exact AF is needed

IVD

RUO

97 % of your tests will return a negative result!

THE ABSENCE OF PROOF IS NOT THE PROOF OF ABSENCE

What does the EU regulation say?

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Chapter II - REQUIREMENTS REGARDING PERFORMANCE, DESIGN AND MANUFACTURE

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Assay implementation - 2 routes possible

CE-IVD labelled product

↓

Verification needed

→

Based on qualified and metrological traceable methods

←

LDT/RUO assay

↓

Validation needed

↓

A comparison needs to be made between the information in the IFU (specifications) and the results of the assay when using **qualified and metrological traceable material** and results should fall into the acceptance criteria as listed in the IFU.

The usage goals (intended use) must be achieved in a reproducible manner and the validation results from testing the workflow against **qualified and metrological traceable material** with several repeats needs to be within the defined LDT's acceptance criteria.

Example road to validated/verified workflow in your lab

Input:

Your assay

Output

Result Sample 1

Result Sample 2

Result Sample 3

Sample 1: 0% allelic frequency (no mutation)

Sample 2: 50% allelic frequency (X mutations = dependent on assay)

Sample 3: 100% allelic frequency (X mutations) = dependent on assay)

No mutation detected?

0% AF detected (within acceptance range)?

Mutation correctly detected?

AF detected (within acceptance range)?

Yes / No

Yes / No

Yes / No

Yes / No

Test reproducibility by repeatedly running this validation

All answers “Yes”?
- Wildtype can be detected

Answers “Yes”?
- Specification fulfilled
- Heterozygous / homozygous mutation detected

One answer “No”?
- Validation failed

Error in workflow
- Error analysis necessary
- Correction actions necessary

Conclusion

- In order to obtain reliable results, either with RUO or CE-IVD assays, labs will need to use metrologically traceable controls as stated in the guidelines.
- Although controls are not always available, efforts must be made by assay developers and end-users to develop and implement such controls.
- Proper use of a control …..
  - can decide what medications to be use best (liquid biopsy, variant detection)
  - can validate your results in recurrence testing thus providing optimal care for treated patients
  - can prevent you from death by medication (DPYD Genotyping)

Can’t find what you are looking for?

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Contact us: info@sens-id.com