OncoDNA®
THE CANCER THERANOSTIC COMPANY

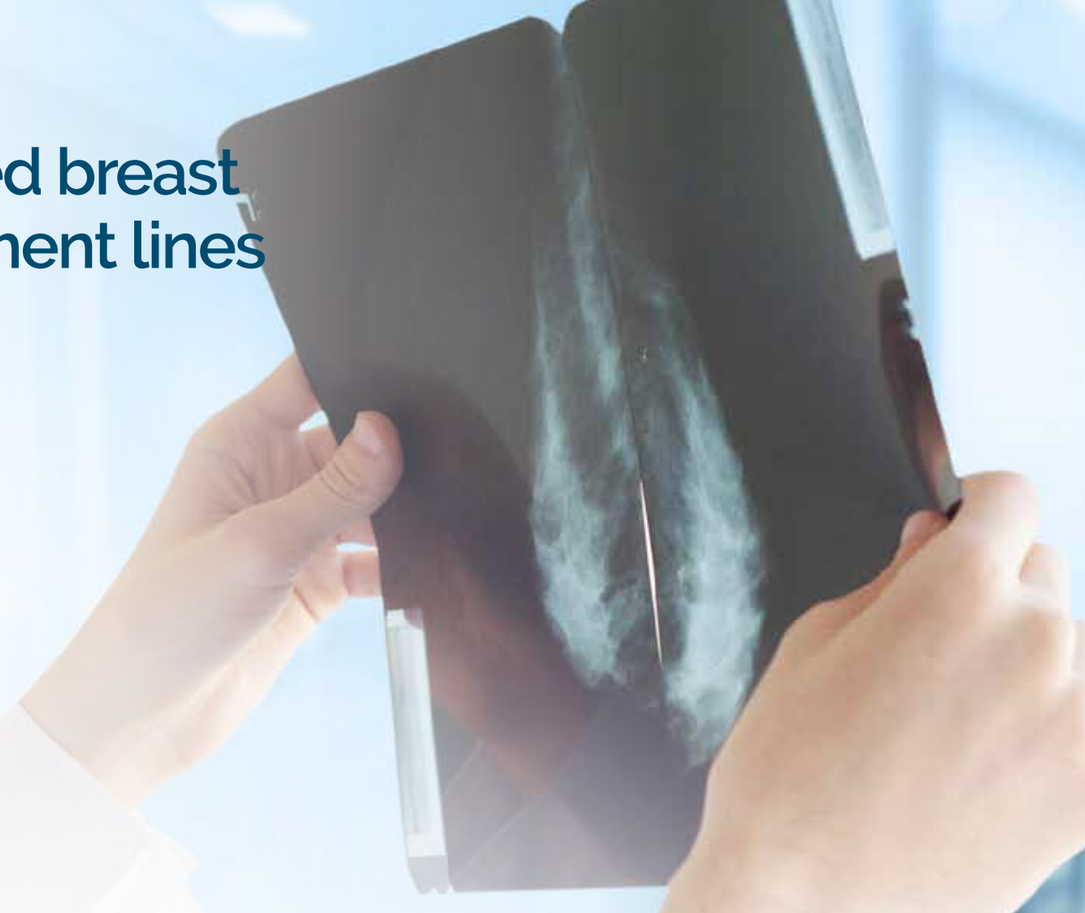
SCREEN MORE THAN THE USUAL SUSPECTS IN

Breast Cancer

CLINICAL EVIDENCE FOR MOLECULAR PROFILING

A unique **combination of power** for decision making

Comprehensive molecular profiling for advanced breast cancer now offers decision support for all treatment lines



Multiple studies have demonstrated the benefit of therapies that are chosen based upon the molecular profile of a tumor. Funda Meric-Bernstam, Chair of the Department of Investigational Cancer Therapeutics, MD Anderson Cancer Center, Houston, Texas. (Kurnit at al 2018)

New insights into breast cancer derived from NGS and other genomic analyses have the potential to improve breast cancer care in myriad ways from improving early detection to better prognostic and predictive markers for early-stage breast cancer to the development of novel therapies for advanced disease. (Scott Heinemann et al 2018)

Today it is clear that molecular profiling of advanced breast cancer tumors is beneficial in assisting clinical treatment plans. (P Carter at al 2018)

SUMMARY OF THE ADVANCED BREAST CANCER ESMO GUIDELINES

			ER-/HER+	ER+/HER+	ER+/HER-	Triple -	Triple -
		ER	−	+	+	−	−
		HER2	+	+	−	−	−
		BRCA				MUT	
FIRST LINE	Chemotherapy	*Taxanes*	✓	✓	(✓)	✓	✓
		Anthracycline	✓	✓	(✓)	✓	✓
		Platinum				✓	✓
	Anti-VEGF	*Bevacizumab*	(✓)	(✓)	×	×	×
	Endocrine therapy	*Tamoxifen, Fulvestrant*	×	×	✓	×	×
	Aromatase Inhibitor	*Anastrozole, Letrozole*	×	×	✓	×	×
	HER2-inhibitors	*Neratinib*	✓	✓	×	×	×
		Trastuzumab	✓	✓	×	×	×
		Pertuzumab	✓	✓	×	×	×
		Lapatinib	×	(✓)	×	×	×
	CDK4/6 inhibitor	*Palbociclib, Ribociclib, Abemaciclib*	×	×	✓	×	×
	MTOR Inhibitor	*Everolimus*	×	×	✓	×	×
	PARP Inhibitor	*Olaparib, Rucaparib, Niraparib*	×	×	×	✓	×
SECOND LINE	Chemotherapy	*Taxanes*	✓	✓	✓	✓	✓
		Anthracycline	×	×	✓	✓	✓
	Endocrine therapy	*Tamoxifen, Fulvestrant*	×	×	✓	×	×
	Aromatase Inhibitor	*Anastrozole, Letrozole*	×	×	✓	×	×
	HER2-inhibitors	*Neratinib*	✓	✓	×	×	×
		Trastuzumab	✓	✓	×	×	×
		Trastuzumab emtansine (T-DM1)	✓	✓	×	×	×
		Lapatinib	✓	✓	×	×	×
	CDK4/6 inhibitor	*Palbociclib, Ribociclib, Abemaciclib*	×	×	✓	×	×
	MTOR Inhibitor	*Everolimus*	×	×	✓	×	×

✓ : recommended treatment (✓) : possible treatment × : not recommended treatment

There are plenty of markers to help find the best fit beyond the 4 usual suspects (ER/PR/HER2/KI67)

RESPONSE PREDICTIONS	TREATMENT FAILURE PREDICTIONS
IHC indicators of response	IHC indicators of resistance
BRCA1 expression	ERCC1 expression
VEGFR2 expression	
Oestrogen receptor expression	ESR1 mutation/fusion, ERBB2 mutation, FGFR amplification
ERBB2 IHC, ERBB2 mutation/amplification	ERBB2 secondary mutation, RAS pathway activation, MET amplification
CDK4/6 amplification, CDKN2A loss	RB1 loss, CCNE1 amplification (to evaluate)
AKT-PI3K pathway activation, p4EBP1 IHC, PTEN IHC	
BRCA1/2 mutation/HRD Pathway mutation	Reversion mutation
IHC indicators of response	IHC indicators of resistance
Oestrogen receptor expression	ESR1 mutation/fusion, ERBB2 mutation, FGFR amplification
ERBB2 activating mutation/amplification	ERBB2 secondary mutation, RAS pathway activation, MET amplification
CDK4/6 amplification, CDKN2A loss	RB1 loss, CCNE1 amplification (to evaluate)
AKT-PI3K pathway activation, p4EBP1 IHC, PTEN IHC	

SOME ILLUSTRATIVE CASES FROM ONCODNA SAMPLE DATABASE

In ER positive patients

Based on NGS data or immunohistochemistry we found for example :

RESISTANCE TO
Capecitabin or **Fluorouracil** in more than **35%** of the samples
Tamoxifen in close to **20%** of the samples
CDK4/6 in **16%** of the samples
Aromatase inhibitors in **10%** of the samples

SENSITIVITY TO
CDK4/6 inhibitors in **27%** of the samples
mTOR inhibitors in **16%** of the samples

In HER2 positive patients

Based on NGS data or immunohistochemistry we found for example :

RESISTANCE TO
Anti HER2 in more than **10%** of the samples
Fluorouracil in more to **50%** of the samples
Nivolumab in **10%** of the samples
Lapatinib in close **10%** of the samples

SENSITIVITY TO
CD4/6 inhibitors in **33%** of the samples
mTOR inhibitors in **10%** of the samples

In triple negative patients

Based on NGS data or immunohistochemistry we found for example :

RESISTANCE TO
Taxanes in **22%** of the samples
Anthracycline in **15%** of the samples
Platinum in **50%** of the samples

SENSITIVITY TO
mTOR inhibitors in **39%** of the samples
Androgen biosynthesis inhibitors in **28%** of the samples
Platinum in **14%** of the samples

In triple negative patients - BRCA positive

Based on NGS data or immunohistochemistry we found for example :

RESISTANCE TO
PARP inhibitors in up to **13%** of the samples

SENSITIVITY TO
mTOR inhibitors in **33%** of the samples
MEK inhibitors in more than **20%** of the samples

UP TO 50% OF HR POSITIVE BREAST CANCERS DO NOT RESPOND TO ENDOCRINE TREATMENTS (OSBORNE CK AT AL, N ENG J MED 1998 339)

We could identify early resistance before starting or during treatment by quickly performing extended molecular profiling including :

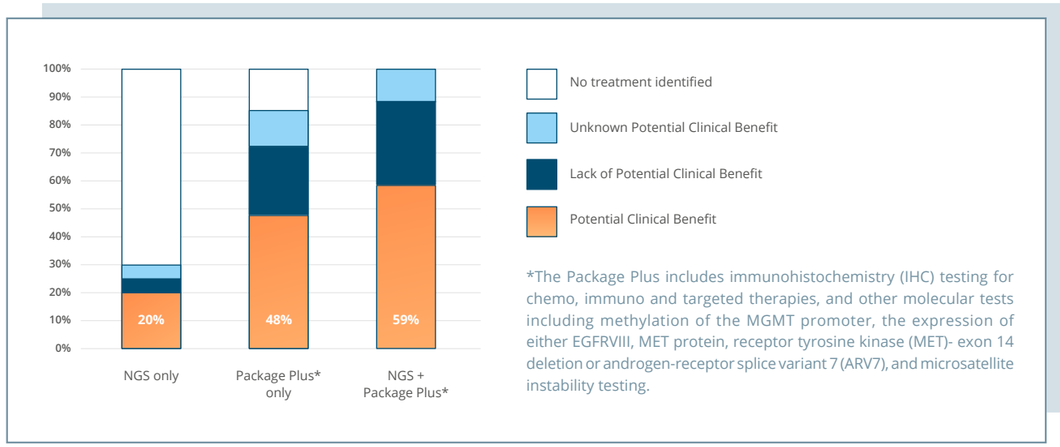
- → **ESR1 mutation or fusion**
- → **ERBB2 mutation**
- → **FGFR amplification**
- → **IGFR1 over-expression**

IHC AND OTHER TESTS ADD INFORMATION

Our data showed that NGS alone provided the oncologist with useful information in 10–50% of cases (depending on cancer type), whereas the addition of IHC/other tests increased extensively the usefulness of the information provided. (Laes et al 2018)

Get three time more insight by combining :

IHC, TMB, HRD testing and RNA data to NGS for breast cancer patients gives for best treatment selection (Laes et al 2018)

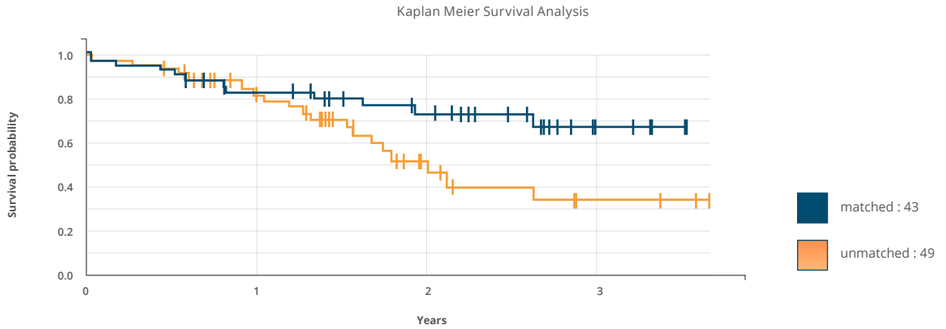


*The Package Plus includes immunohistochemistry (IHC) testing for chemo, immuno and targeted therapies, and other molecular tests including methylation of the MGMT promoter, the expression of either EGFRVIII, MET protein, receptor tyrosine kinase (MET)- exon 14 deletion or androgen-receptor splice variant 7 (ARV7), and microsatellite instability testing.

EXTENDED TUMOR MOLECULAR PROFILING IMPROVES THE SURVIVAL OF BREAST CANCER PATIENTS BY 31% (P CARTER AT AL 2018)

Based on a retrospective review of a cohort of patients that were profiled using established IHC biomarkers, along with fragment analysis, in situ hybridization and sequencing.

By comparing the group who received treatment according to molecular profiling with the group who did not, they showed that the matched treatment group had an increase in survival of 31% compared to the average for the unmatched group, an increase of 157 days, from 510 to 667 days (P=0.0316).



A Kaplan-Meier curve showing the increase in overall survival from time of profiling for those patients treated only with therapies predicted to be of benefit by their molecular profile, compared to those patients who received at least one therapy predicted to lack benefit.

Real case report : HR+ breast cancer

PROFILE:

- 48 year-old woman
- Diagnosed 2 years ago with HR+ breast cancer
- Breast cancer with liver and nodal disease
- Stage IV

PREVIOUS SYSTEMIC THERAPIES:

- Palitaxel
- Avastin
- Letrozole
- Palbociclib
- Capecitabine
- Denosumab

OncoSTRAT&GO profiling revealed a mechanism of resistance to hormone therapy and identified everolimus as a potential therapeutic option. Clinical trial opportunities are also highlighted.

SOLID BIOPSY

NEXT GENERATION SEQUENCING:

- **MTOR inhibitor sensitivity**: PIK3CA damaging mutation

IMMUNOHISTOCHEMISTRY:

- **IGF1R inhibitor**: We identified high expression of IGF1R. High expression of IGF1R has been reported as an mTOR inhibition compensatory mecanism leading to the activation of AKT
- **Resistance to hormone therapy**: high expression of IGF1R is associated with resistance to hormone therapy. But as this patient was discover ESR1 wild type, the treatment based on ER inhibitors could be associated with potential benefit for this patient
- **MTOR inhibitor sensitivity**: With high expression of p4EBP1 protein, we have consistent results pointing to activation of the mTOR pathway
- **PI3K/mTOR inhibitors**: PTEN loss predicts sensitivity to inhibitors of the PI3K/Akt/mTOR pathway.
- **PIK3CA or AKT drugs**: We also identified a damaging PIK3CA variant (E542K). Treatment based on PIK3CA or AKT drugs might be associated with clinical benefit for the patient
- **CDK4/6 inhibitor sensitivity**: We showed positive expression of phospho RB1. Therefore treatment based on CDK4/6 inhibitors could be associated with clinical benefit for this patient
- **Resistance to anthracyclines**: With a low/negative expression of TOP2A, treatment based on TOP2A inhibitors (anthracyclines) could be associated with lack of benefit for the patient

LIQUID BIOPSY

NEXT GENERATION SEQUENCING:

- **PI3K inhibitor sensitivity**: PIK3CA activating mutation. The PI3K alpelisib has shown efficacy in a phase 3 clinical trial
- **Advice on ESR1 monitoring:** Some studies have reported that patient with an activating PIK3CA mutation are more susceptible to acquire a mutation in ESR1 that leads to resistance to some ER inhibitors and aromatase inhibitors. Therefore, a monitoring thorough for instance liquid biopsy might be made to look after mutations in ESR1

Earlier **OncoSTRA&GO** profiling may have been **beneficial** for this patient by **reducing the time taken to access** the optimal drug combination.

A lot more
than the **usual**
hospital routine...

Only OncoDNA can combine all this information in solid & liquid biopsies

- → **Improving treatment accuracy in comparison to NGS alone**
- → **Easing the physician adherence to recommendations**
- → **Significantly improving OS (overall survival)**

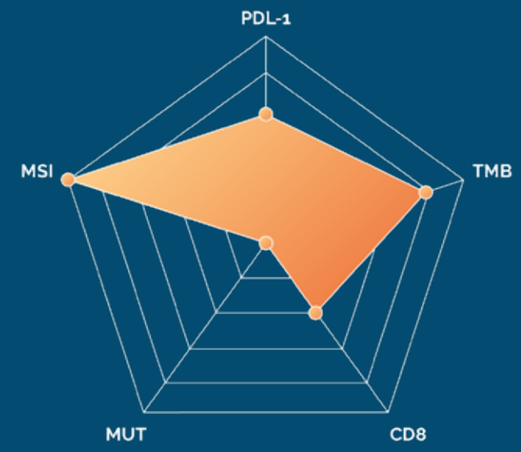
GENES AND GENE REGIONS FOR SOLID AND LIQUID BIOPSIES

• Anti Estrogen tamoxifen, fulvestrant, exemestane, ...	ESR1 · RB1 · FGFR1/2/3 · ER · PR	DNA + Protein
• Anti HER2 trastuzumab, pertuzumab, ...	ERBB2 (HER2) · PIK3CA	DNA
• Platinum carboplatin, ...	ERCC1 · HER2 · BRCA	DNA + Protein
• Chemotherapy Taxane, 5-FU, TOP2A, ...	TOP2A · TLE3 · TS · PGD	DNA
• Anti PD1/PDL1 pembrolizumab, ...	Tumor Burden · MSI · POLE · POLED1 · PDL1 · CD8	DNA + Protein
• MTOR inhibitors everolimus, ...	MTOR · TSC1 · TSC2 · PTEN · PURBP1	DNA + Protein
• CDK4/6 inhibitors Palbociclib, ribociclib, abemaciclib, ...	PRB1 · CDK4 · CDK6 · RB1 · CDKN2A	DNA + Protein
• PI3K inhibitors Alpelisib	PIK3CA	DNA

XXX : Usual hospital routine · DNA/RNA · : Protein

A comprehensive test to give you a **clear and more precise** vision

An unique Immunogram to select the best treatment



Our immunogram is created based on 5 key points, **PD-L1** % (FDA), **TMB** (ASCO 2017), **CD8** T-cell infiltrate (ASCO 2017), **MSI** (FDA) and **Sensitivity/Resistance mutations** (ASCO 2017). With these tools, we are able to give you a clear vision of the potential clinical response of your patient.

The best combination of profiling on the market for

- → **The most comprehensive approach to characterise ICP (immune checkpoint) inhibitor treated patients**
- → **Multifactor and integrative approach with a single partner**
- → **The right molecular profiling combination for ICP**

5 PARAMETER IMMUNOGRAM

1. **Expression of PD-L1**
   This is the first FDA approved biomarker. Although several antibodies exist to detect PD-L1 expression, only PD-L1 IHC 22C3 pharmDx (Dako) is approved as a companion diagnostic for pembrolizumab. Dako's PD-L1 IHC 28-8 pharmDx is approved as a complementary diagnostic for nivolumab. These two antibodies and others are available at OncoDNA.

2. **CD8 T-cell infiltrate as detected by IHC**
   The presence of CD8+ lymphocytes has been associated with better clinical outcomes for patients treated with ICP inhibitors.

3. **Tumor mutational burden (TMB)**
   TMB is a measurement of the mutations carried by tumor cells (number of mutations by units of coding area) and it correlates with higher level of neoantigens. High TMB has been associated with better response and increased survival rate for patients treated with ICP inhibitors.

4. **Microsatellite instability (MSI)**
   MSI, a type of genomic instability, is characterised by gains or losses of nucleotides from microsatellite tracts. It results from impaired DNA mismatch repair (MMR) and MSI-H(igh) status has been associated with high response rates and survival benefit for patients treated with checkpoint inhibitors.

5. **Mutations associated with sensitivity or resistance to ICP inhibitors**
   Mutations associated with sensitivity (e.g. POLE inactivating mutations) or resistance (e.g. STK11 inactivating mutations) to ICP inhibitors. We can test this continuously growing number of variants associated with an impact on immunotherapy.

Which OncoDNA solutions?

We use a combination of the most relevant molecular technologies to support oncologists in their decisions for patient treatment.

Our innovative approach is to combine next-generation sequencing (NGS) with immunohistochemistry (IHC) and additional techniques. This gives a comprehensive view of the tumor profile at the DNA, RNA and protein levels and can help identify more therapeutic options for the patient. Moreover, in 2016 we included liquid biopsy analyses in our solution portfolio, either in combination with solid biopsies or as standalone.

SOLID BIOPSY:

OncoDEEP®

COST-EFFECTIVE SOLUTION COMBINING DNA, RNA AND PROTEIN ANALYSIS OF A TISSUE SAMPLE

OncoDEEP analyses solid biopsies by combining next-generation sequencing (313 genes), IHCs to study protein expression and additional tests. This complete tumor profiling allows to predict patient response to approved or experimental targeted drugs, immunotherapies and chemotherapies.

The NGS panel is accurately designed according to oncologists' needs in their current practice. Importantly, it also includes an accurate determination of MSI, TMB and LOH. The NGS panel is regularly updated based on new findings reported in literature in order to provide patients with the most cost-effective solution.

MATERIAL

• 1 block or 25 slides (5 µm on SuperFrost Plus)

RECOMMENDED FOR :

- All solid tumors (stage III or IV) in adults
- Glioblastoma in children

SOLID AND LIQUID BIOPSIES:

THE COMPLETE SOLUTION INTEGRATING THE ANALYSIS OF SOLID AND LIQUID BIOPSIES

OncoSTRAT&GO is an integrated approach that combines the analyses of a solid biopsy (by next-generation sequencing (313 genes), IHCs and additional tests) with the analysis of a blood biopsy. The blood profiling focuses either on the circulating tumor DNA (for deciphering tumor heterogeneity) or in DNA from blood cells (for studying specific germline gene alterations related to BRCAness phenotype that are challenging to detect in FFPE samples).

OncoSTRAT&GO establishes a complete genetic profile of the tumor, which can be used to identify sensitivity or resistance to targeted therapies, chemotherapies and immunotherapies.

MATERIAL

• 1 blood sample (1x10 ml Streck tube or 1x10 ml EDTA tube)
• 1 block or 25 slides (5 µm on SuperFrost Plus)

RECOMMENDED FOR :

The following stage IV solid tumors in adults:
- Non-small cell lung cancer
- **HR+, HER2+ and triple-negative breast cancer**
- Colorectal cancer
- CUP
- Ovarian cancer
- Pancreatic cancer

NO SOLID BIOPSY:

OncoSELECT®

CANCER-SPECIFIC SOLUTION FROM A LIQUID BIOPSY SAMPLE

OncoSELECT is a fast and minimally invasive analysis of circulating tumor DNA from a blood sample.

It is the perfect solution to identify therapeutic options for cancer patients not able to have their tumor biopsied or whose biopsy is too old. It can be used as a tool to detect treatment resistance to targeted therapies (before first-line to check the heterogeneity of the disease, or during/after treatment to check for acquired resistance mutations), as well as for monitoring cancer progression.

MATERIAL

• 2 blood samples (2x10 ml Streck tubes)

RECOMMENDED FOR :

The following metastatic solid tumors in adults:
- Non-small cell lung cancer
- Breast cancer HR+ or HER2+
- Colorectal cancer

MONITORING RESPONSE:

OncoDNA can also provide other kinds of monitoring tools according to cancer type.

Do not hesitate to request more information or our support at **sales@oncodna.com**

Update of our solid panel part !

Our solid panel used alone (OncoDEEP) or in the mixed liquid/solid solution (OncoSTRAT&GO) is the most comprehensive profiling for solid tumor combining DNA and protein data.

The solid panel profiles solid tumor samples by **sequencing** an extensive variety of genes linked to approved targeted therapies, combined with **IHC** tests to detect important **proteins** and with other tests, such as **MSI**, **gene fusion** and promoter methylation. The NGS panel is based on an accurate analysis of oncologists' needs in their current practice when the choice of solutions is reduced for the patients. The panel is updated every year based on advances reported in literature, so as to provide patients with the most economical and effective solutions. **The solid panel** provides information about approved or in development hormonal therapies, immunotherapies (through a personalized immunogram) and chemotherapy, as well as targeted therapies.

The best combination of profiling on the market for

→ **Immunotherapy**
→ **Targeted therapy**
→ **Chemotherapy**

} **selection**

WHAT IS NEW?

- 4x more genes and gene regions (313) for more acurate immunotherapy selection
- Broader microsatellite instability (MSI) and tumor mutational burden (TMB) coverage to increase the accuracy of our algorithm
- SNP: The most powerful panel for the best immunotherapy selection
- Broader fusion panel detection. Beyond the usual suspects

How to order a test ?

1 1. LOGIN TO OncoSHARE by OncoDNA

OncoSHARE: An easy way to access & order your tests and receive the personalised report on treatment recommendation

When you join **OncoSHARE**, you become a member of an active network gathering together more than 13 000 patients and oncologists.

Regardless of whether information concerns patient health or payment, we take every precaution to ensure your security. OncoSHARE is used by oncologists to order our solutions, display interactive analysis reports and connect health care professionals to each other and to our team of experts.

In a simple, interactive manner, **OncoSHARE** will guide you in your selection of the most appropriate treatment options based on the unique signature of your patient's tumor.

www.oncoshare.com

2 2. ORDERING AN ONCODNA SOLUTION

2.1 Mention the person to bill - (credit card or wire transfer possible)
2.2 Select the kit you want to use and if we need to ship it to you
2.3 Describe the clinical state of your patient
2.4 We ship the corresponding sample collection kit to you

3 3. COLLECT THE SAMPLE

Send the kit back to OncoDNA (free of charge). Please print your own prepaid shipping label generated online at https://delivery.oncodna.com.

4 4. SAMPLE ANALYSIS

Upon arrival at the OncoDNA facilities, the sample quality is checked and the sample is recorded in our tracking system for further analysis.

5 5. YOUR REPORT READY ON ONCOSHARE

After interpretation by our experts, the results are published in an interactive report which is made available to you through your OncoSHARE account.

6 6. WE SUPPORT YOU

Support is available at all times, for patients through our Patient Care department **(infos@oncodna.com)** and for oncologists via our scientific team **(molecular@oncodna.com).**

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CLINICAL EVIDENCE FOR MOLECULAR PROFILING

A unique **combination of power** for decision making

ONCODNA'S SOLUTION CAN ALSO BE OF HELP WITH MANY OTHER CANCER TYPES :

HEAD & NECK • BLADDER • PROSTATE • CANCER OF UNKNOWN PRIMARY •
COLORECTAL • NSCLC • MELANOMA • ...

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