AI and tumor molecular profiling

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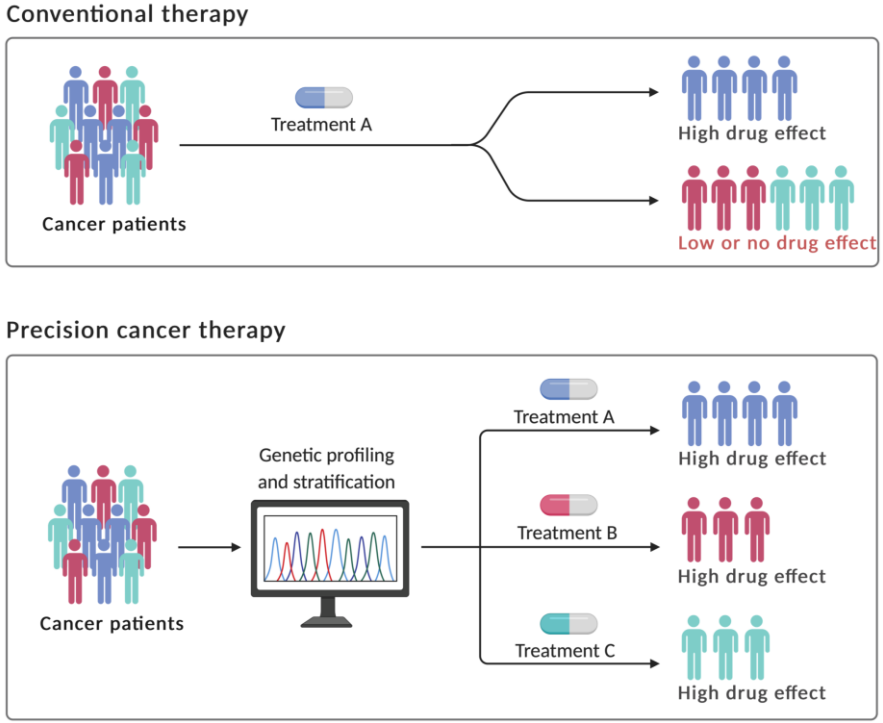
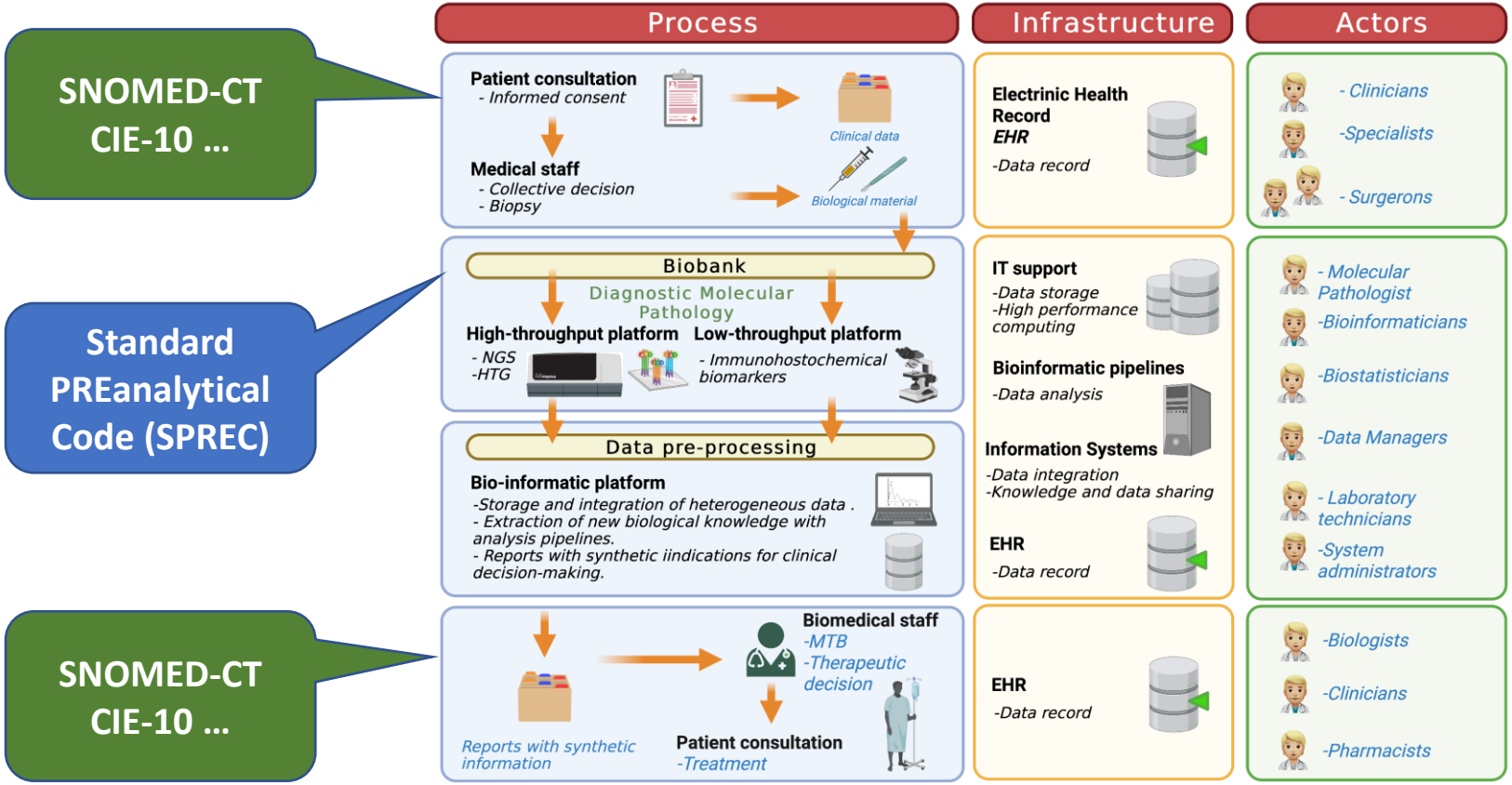
Outline

- Precision medicine
- MPD©
- SCARFACE
- Conclusions

- **Precision medicine** constitutes an approach for **disease treatment and prevention** that takes into account **individual genetic variability**, **environment**, and **lifestyle for each person**.
- This approach will **allow to predict more accurately which treatment and prevention strategies for a particular disease will work in which groups of people**.





Adapted from Servant N, et al. Front Genet. 2014 May 30;5:152

- IVO and HTG have signed an agreement of collaboration for the development of diagnostic molecular tools.

•***Mamapred© (MPD©)*** has been developed by Fundación Instituto Valenciano de Oncología, Fundación Pública Andaluza Progreso y Salud, and Consorcio Centro de Investigación Biomédica en Red, M.P.

Aim of MPD

To **develop and validate** a molecular test to determine **the risk of relapse in patients with early-stage HR+/HER2- breast cancer**, by **defining a relapse score from data generated with the HTG EdgeSeq Oncology Biomarker Panel** from breast cancer cases previously analyzed with the recurrence score of the OncotypeDx® and MammaPrint® platforms.

AGENDIA MAMMAPRINT+BLUEPRINT

MINDACT trial

In conclusion, in a large group of patients at high clinical risk for breast-cancer recurrence, the addition of the 70-gene signature to the traditional clinical and pathological factors provided valuable information for considering which patients might benefit from adjuvant chemotherapy. We found that chemotherapy with its attendant toxic effects could be avoided in these patients at high clinical risk but low genomic risk at a cost of a risk of distant metastasis at 5 years that is 1.5 percentage points higher. Follow-up is ongoing to determine whether these conclusions remain valid for longer-term outcome.

ONLY PATIENTS CLASSIFIED AS HIGH RISK, INDEPENDENTLY OF THE CLINICAL RISK WOULD BE BENEFITED BY CHEMOTHERAPY

Cardoso F et al. N Eng J Med 2016; 375(8):717-29

oncotype DX® Breast Cancer Assay

TAILORx trial

CONCLUSIONS

Adjuvant endocrine therapy and chemoendocrine therapy had similar efficacy in women with hormone-receptor–positive, HER2-negative, axillary node–negative breast cancer who had a midrange 21-gene recurrence score, although some benefit of chemotherapy was found in some women 50 years of age or younger. (Funded by the National Cancer Institute and others; TAILORx ClinicalTrials.gov number, NCT00310180.)

ONLY PATIENTS CLASSIFIED AS HIGH RISK ARE BENEFITED BY CHEMOTHERAPY

WOMEN 50 YEARS OF AGE OR YOUNGER CLASSIFIED AS INTERMEDIATE-RISK MIGHT BENEFIT BY CHEMOTHERAPY

Sparano JA et al. N Eng J Med 2018; 379(2):111-121

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Inclusion critera:

Women with an IDC of the breast that meets the followin criteria:

CLINICAL CRITERIA (all must be met):

- ✓ Women < 75 yo
- ✓ Complete surgerey (< 8 weeks)
- ✓ ER/PR + and HER2 -
- ✓ pT (TNM): pT1 or pT2
- ✓ pN (TNM): pN0 or pN1 microinfiltrant

Risk CRITERIA: (at least one of the following must be present)

- ✓ ER immunostaining Low/Moderate [+/++], [1 - 60%].
- ✓ PR negative (<1%)
- ✓ Histological grade II
- ✓ Intermediate Ki67: 14% - 30%

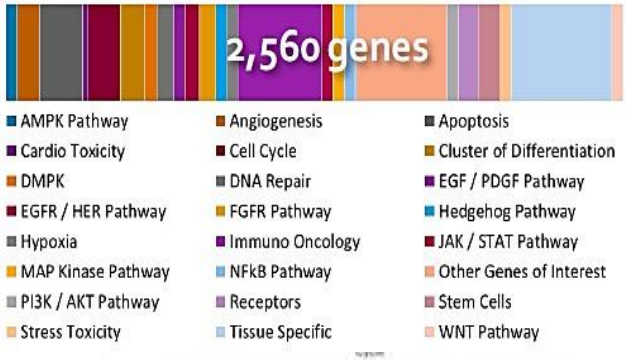
All cases should have been tested with any of the Platforms MammaPrint or OncotypeDx.

ivo — MP/OT

Hospital Universitario Ramón y Cajal, SaludMadrid, Comunidad de Madrid — MP

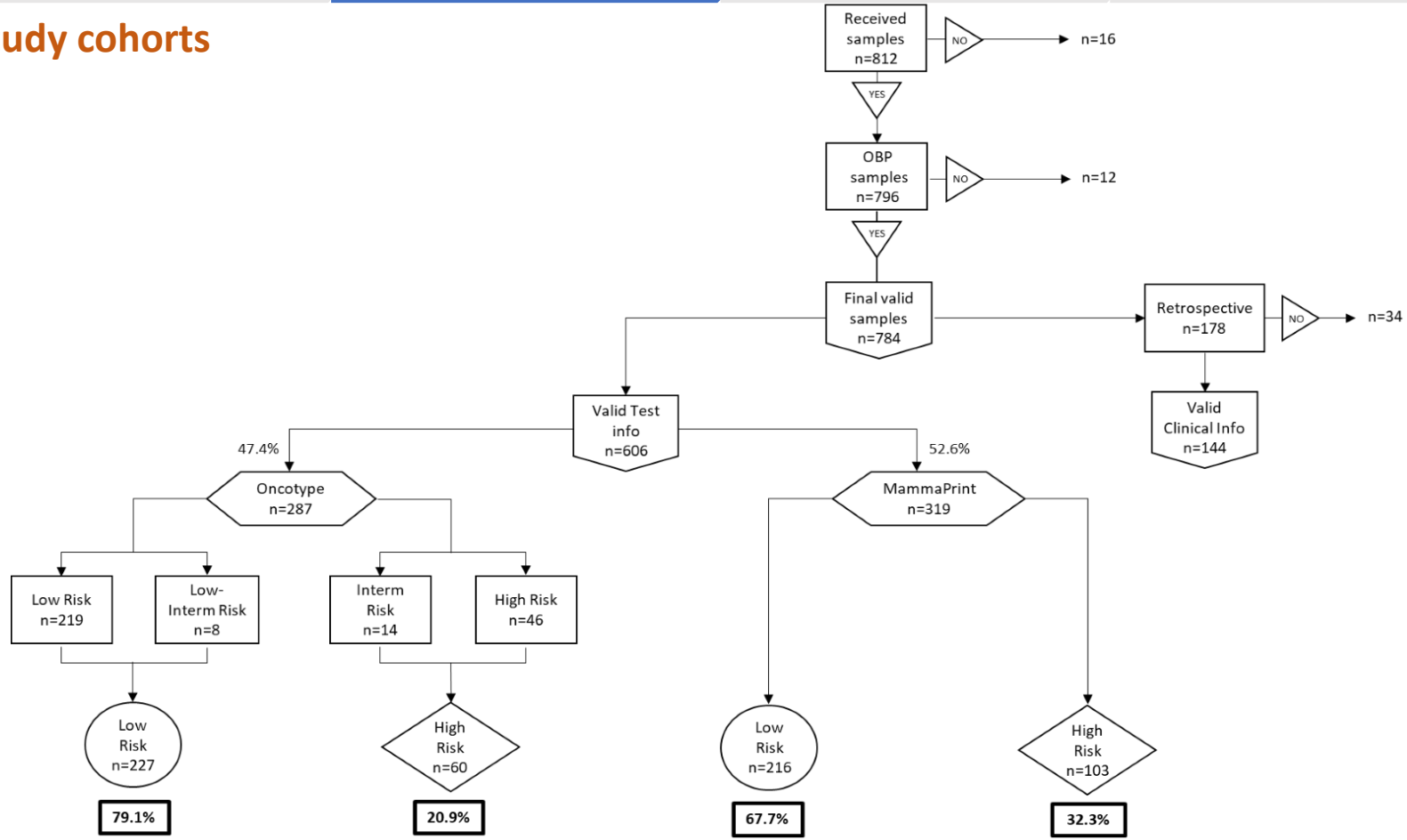
Hospital del Mar, Parc de Salut MAR Barcelona, HOSPITAL DEL MAR — OT

RVB Red Valenciana de Biobancos — MP/OT



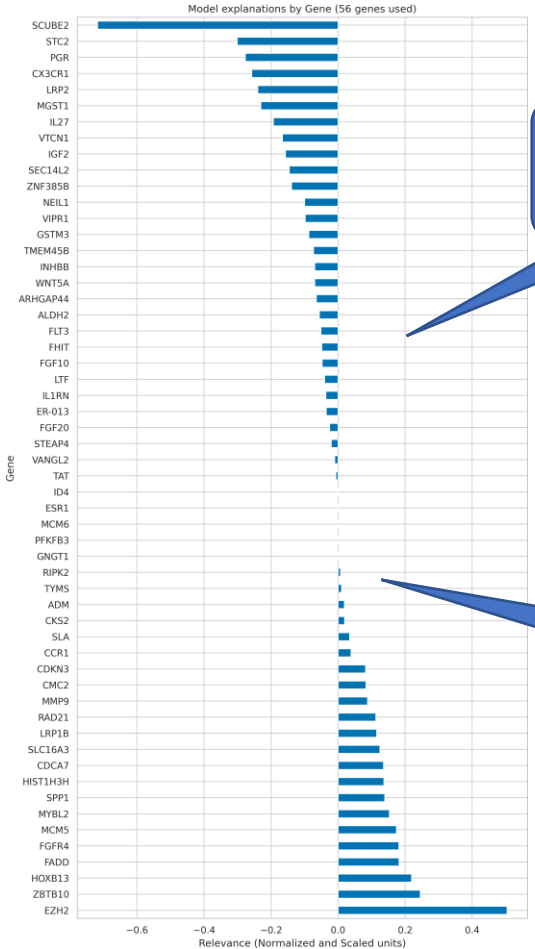
5 µm-thin FFPE sections and 15 mm^2 tumor area

Study cohorts



Analytical Validation

	aupr	balanced_accuracy
log_minmax_merge	• 0.731198	• 0.81354
log_minmax_mp	• 0.81749	• 0.80226
log_minmax_ot	• 0.79984	• 0.81354
log_wos_merge	• 0.79388	• 0.79705
log_wos_mp	• 0.8155	• 0.80010
log_wos_ot	• 0.75805	• 0.8072
rmbatch_minmax_merge	• 0.75051	• 0.76843
rmbatch_minmax_mp	• 0.74424	• 0.77306
rmbatch_minmax_ot	• 0.81429	• 0.82243
rmbatch_wos_merge	• 0.793832	• 0.78707
rmbatch_wos_mp	• 0.74945	• 0.77345
rmbatch_wos_ot	0.73119	0.81354



Insulin receptor signaling cascade IGFR1 and PIK3CA pathway

Pathways in cancer and breast cancer

J Clin Oncol 39, 2021 (suppl 15; abstr 558)

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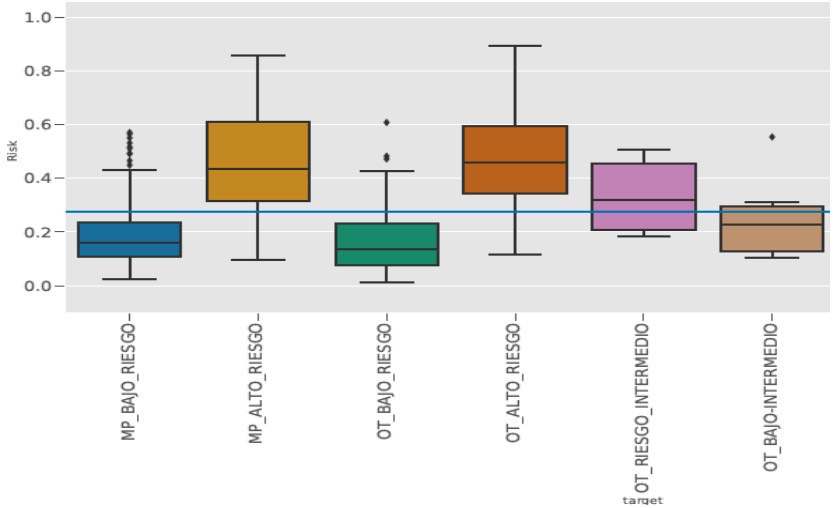
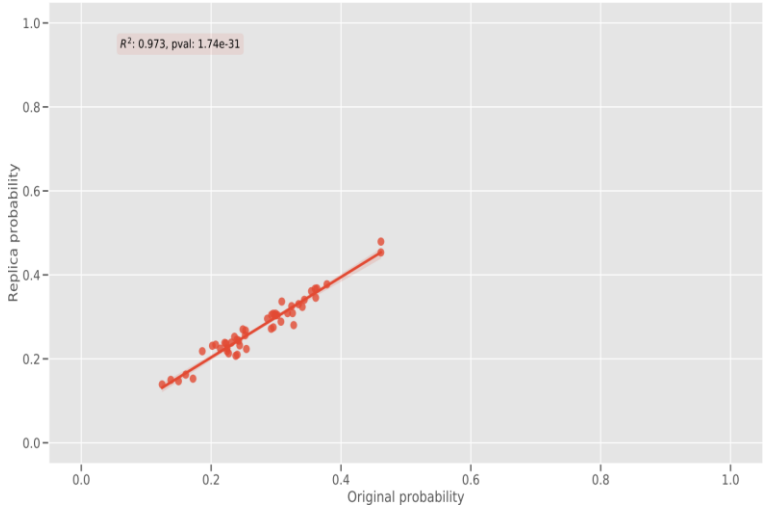
Metrics

Balanced accuracy, 80.5%;
Kappa, 0.562;
Specificity, 80.7%; and
NPV, 91.4%.





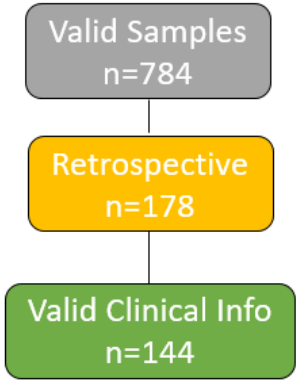
J Clin Oncol 39, 2021 (suppl 15; abstr 558)

Clinical Validation

Retrospective validation

- n=144
- Prognosis
- Systemic relapse (15/129)
- More tan 10 years follow-up
- Early stages
- Luminal cases
- No tested with OT or MP

Parameters	Breast Cancer Patients
Age (years), n	144
mean (range)	62,91 (33-89)
cT (mm), n	141
T1	118 (83,6%)
T2	19 (13,4%)
T3	2 (1,4%)
T4	1 (0,7%)
Unknown	1 (0,7%)
cN, n	144
Negative	132 (891,6%)
Positive	11 (7,6%)
Hormonal Receptor status, n	143
Negative	1 (0,6%)
Positive	142 (99,3%)
cERB2, n	143
+	102 (71,3%)
++	17 (11,8%)
+++	11 (7,7 %)
Unknown	13 (9,1%)
Grade, n	102
1	43 (42,1%)
2	30 (29,4%)
3	5 (4,9%)
Unknown	24 (23,5%)
Follow-up (years), n	144
mean (range)	10,53 (3,100-23,10)
PFS (months), n	144
mean (range)	311,98 (32,25 – 591,58)
MFS (months), n	144
mean (range)	314,42 (32,25 – 591,58)
OS (years), n	144
mean (range)	10,53 (3,13 – 23,07)
Relapse, n	144
Negative	138 (95,8%)
Positive	6 (4,2%)
Sistemic Relapse, n	144
Negative	129 (89,5%)
Positive	15 (10,5%)
Contralateral Breast Tumor, n	144
Negative	139 (96,5%)
Positive	5 (3,5%)
Histology, n	94
IDC	65 (69,1%)
ILC	10 (10,6%)
Tubular	7 (7,4%)
Other	12 (12,7%)



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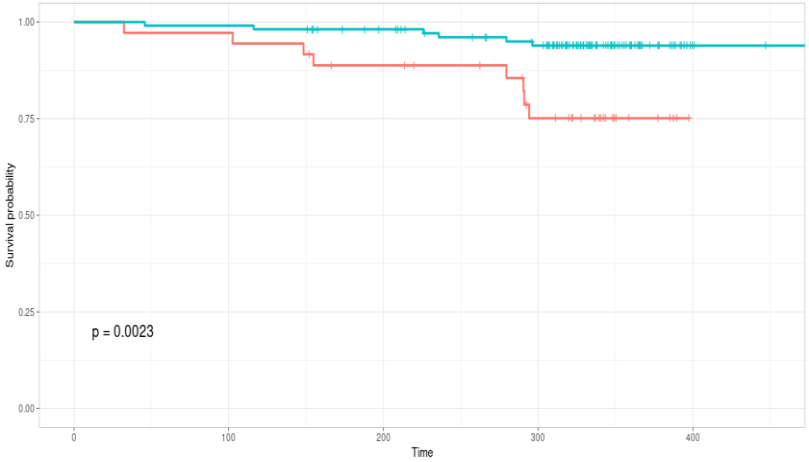
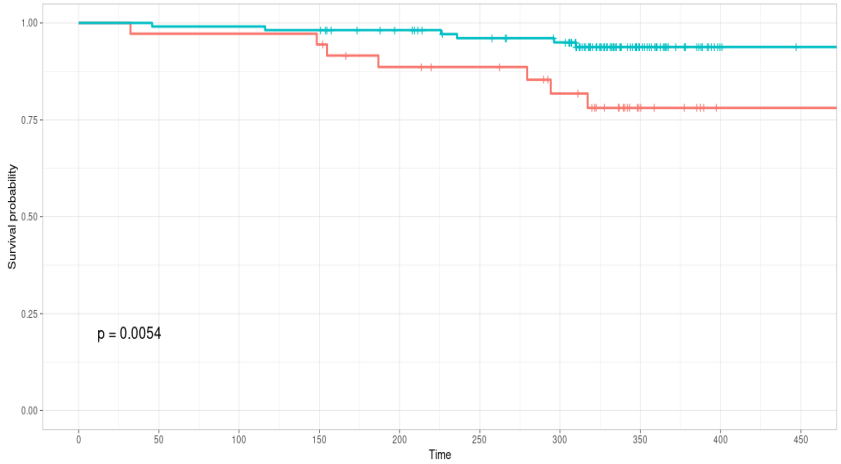
Clinical Validation

Local relapse



Systemic relapse



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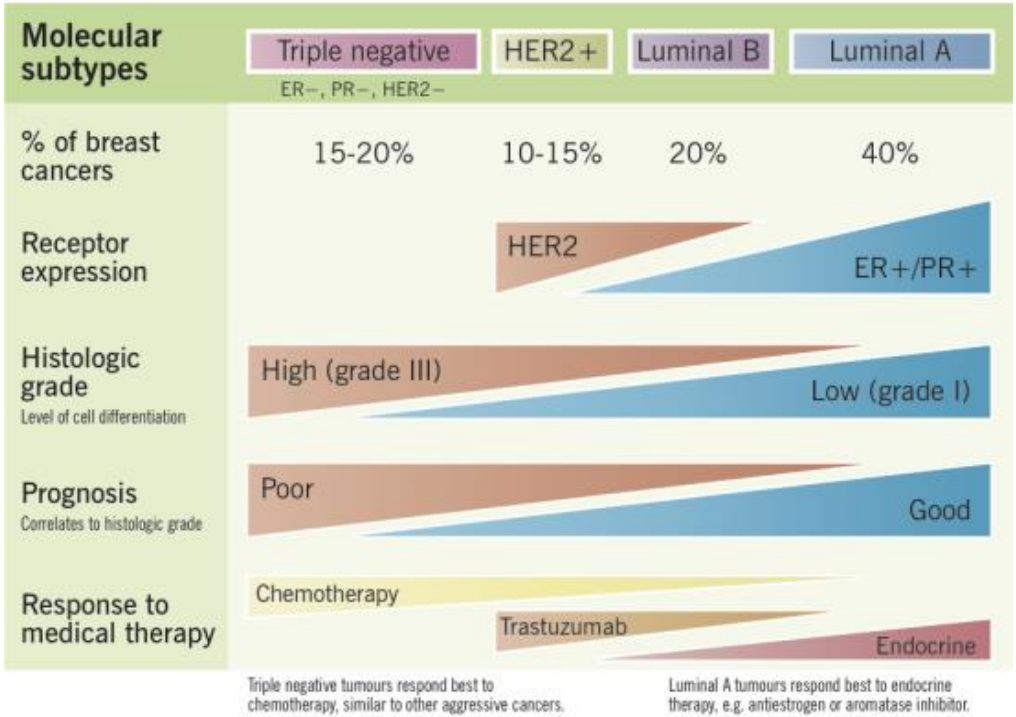
Absolute Intrinsic Molecular Subtyping (AIMS)



- Why is importat a molecular classification?
  - Diagnosis
  - Prognosis
  - Treatment
- **PAM50 classifies BC in 5**: *Luminal A*, *Luminal B*, *Normal-Like*, *Her2 Enriched* and *Basal.*
  - Nanostring nCounter
  - Closest distance of 50 gene expression
  - May be influenced by the cohort used

Harbeck, N., Penault-Llorca, F., Cortes, J. et al. Breast cancer. Nat Rev Dis Primers 5, 66 (2019).

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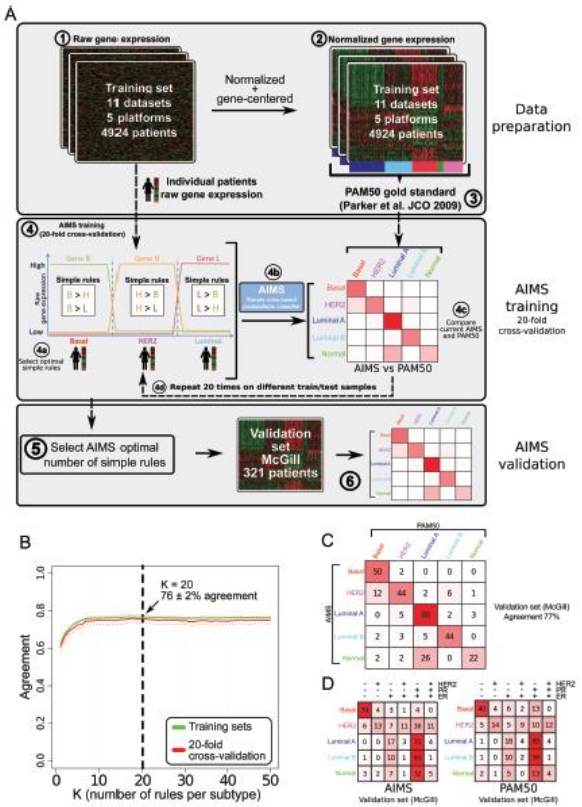
Absolute Intrinsic Molecular Subtyping (AIMS)

- The **AIMS algorithm** is implemented in both the **GeneFu** and **AIMS R packages** available in **Bioconductor**.
- Redefine a **stable single sample absolute version of PAM50**
- It works by comparing the gene expression of **151 genes** in a series of 100 binary rules.
- **Less dependent** on the technology platform used.
- Like PAM50, AIMS classifies the samples into the 5 intrinsic subtypes.
- Among the **151 analyzed genes 89 (58.9%) are represented in HTG OBP panel comprising 41 of 100 (41%) decision rules**, which are still enough to reliable assign an intrinsic subtype to the breast cancer sample.



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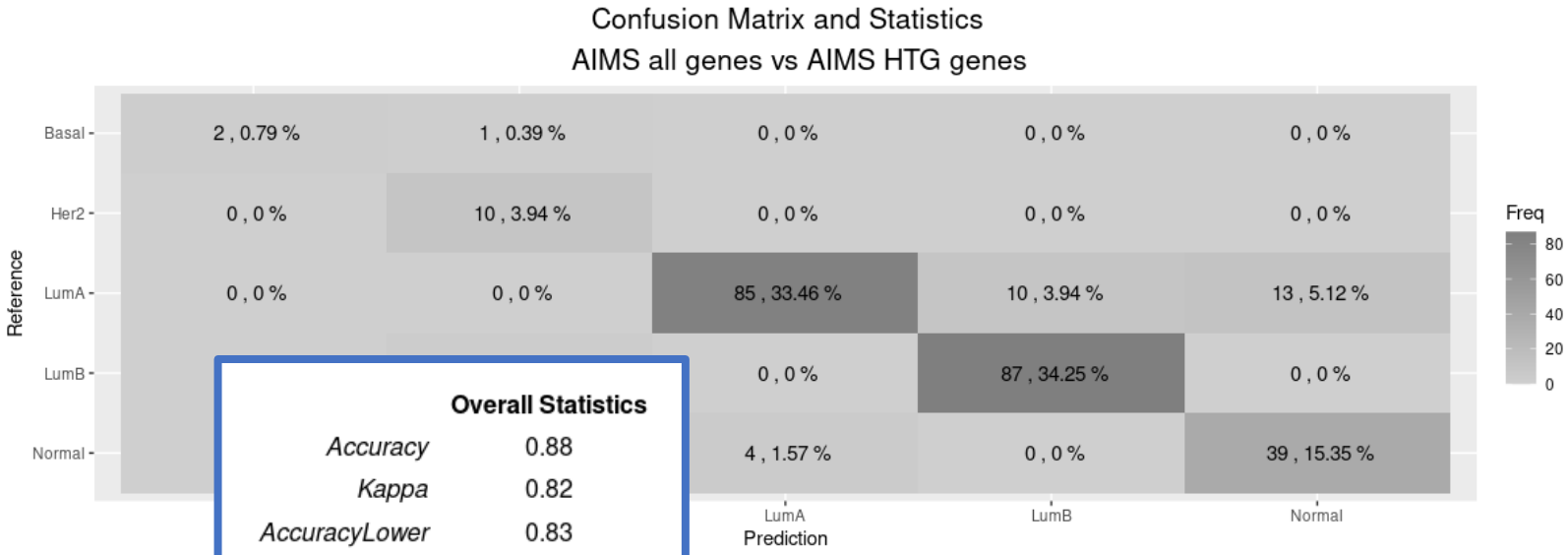
Absolute Intrinsic Molecular Subtyping (AIMS)



Overall Statistics	
Accuracy	0.88
Kappa	0.82
AccuracyLower	0.83
AccuracyUpper	0.92
AccuracyNull	0.43
AccuracyPValue	0
McnemarPValue	NaN

Predictive-Response Model to DNA-damaging agents based on genomic scars

SCARFACE

Grupo Español de Investigación en Cáncer de Ovario

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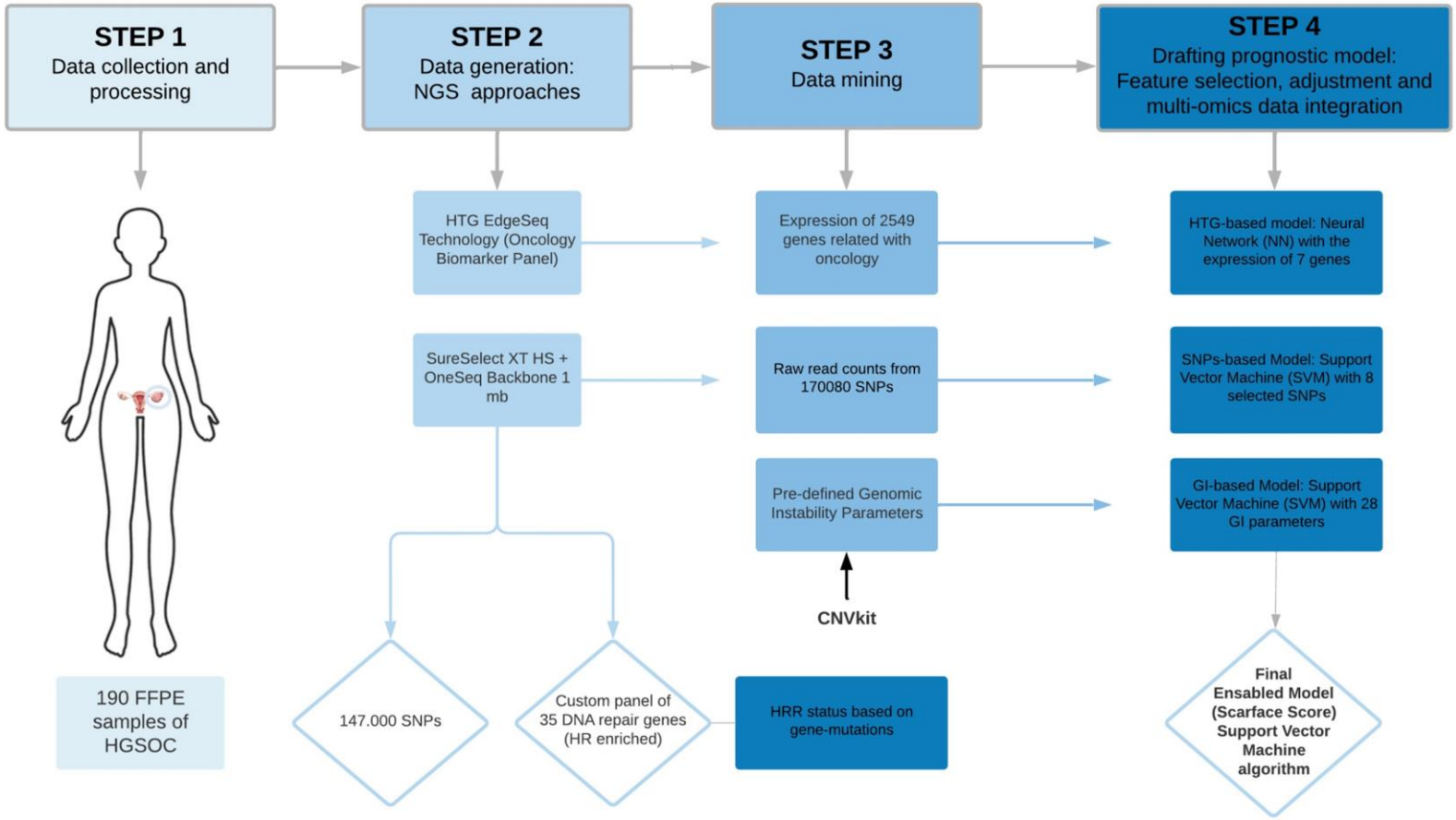
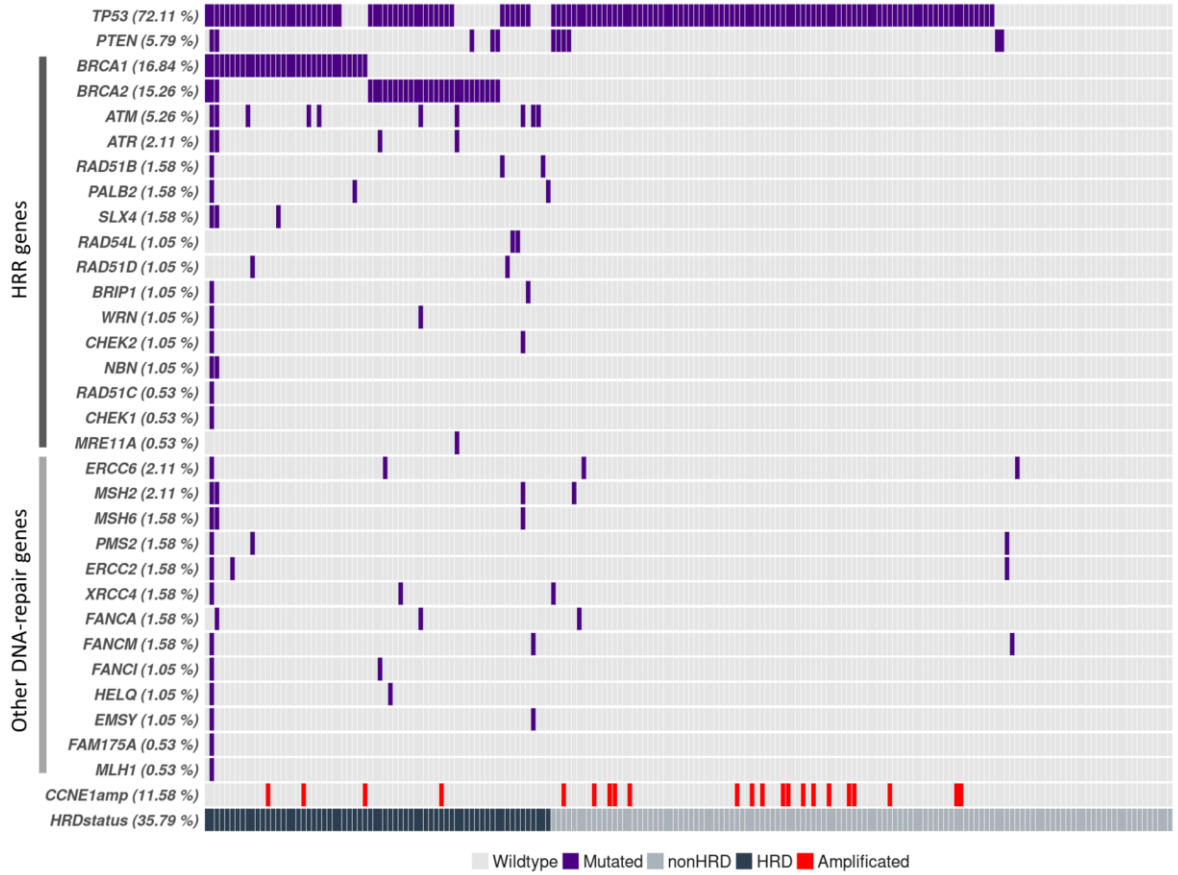

STEP 1
Data collection and processing
STEP 2
Data generation: NGS approaches
STEP 3
Data mining
STEP 4
Drafting prognostic model: Feature selection, adjustment and multi-omics data integration
190 FFPE samples of HGSOC
HTG EdgeSeq Technology (Oncology Biomarker Panel)
Expression of 2549 genes related with oncology
HTG-based model: Neural Network (NN) with the expression of 7 genes
SureSelect XT HS + OneSeq Backbone 1 mb
Raw read counts from 170080 SNPs
SNPs-based Model: Support Vector Machine (SVM) with 8 selected SNPs
Pre-defined Genomic Instability Parameters
GI-based Model: Support Vector Machine (SVM) with 28 GI parameters
CNVkit
147.000 SNPs
Custom panel of 35 DNA repair genes (HR enriched)
HRR status based on gene-mutations
Final Ensabled Model (Scarface Score) Support Vector Machine algorithm

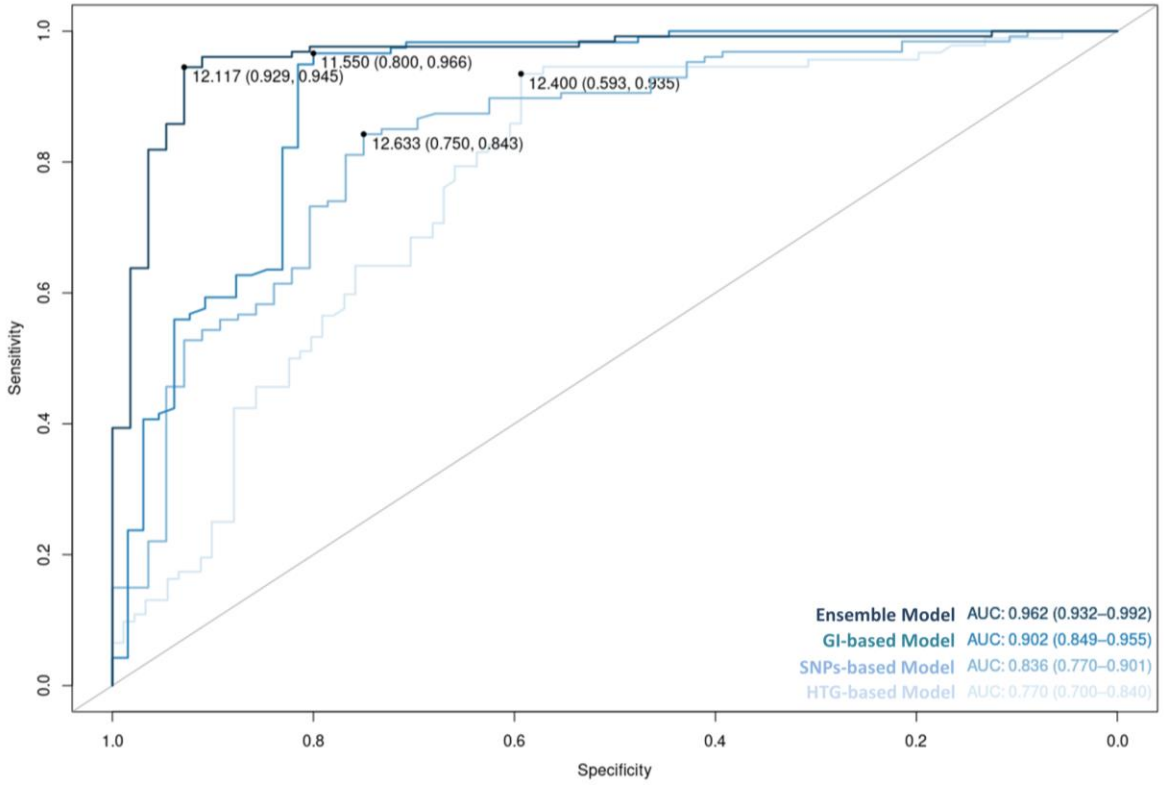
DistrIbution of genetic alterations of DNA repair genes



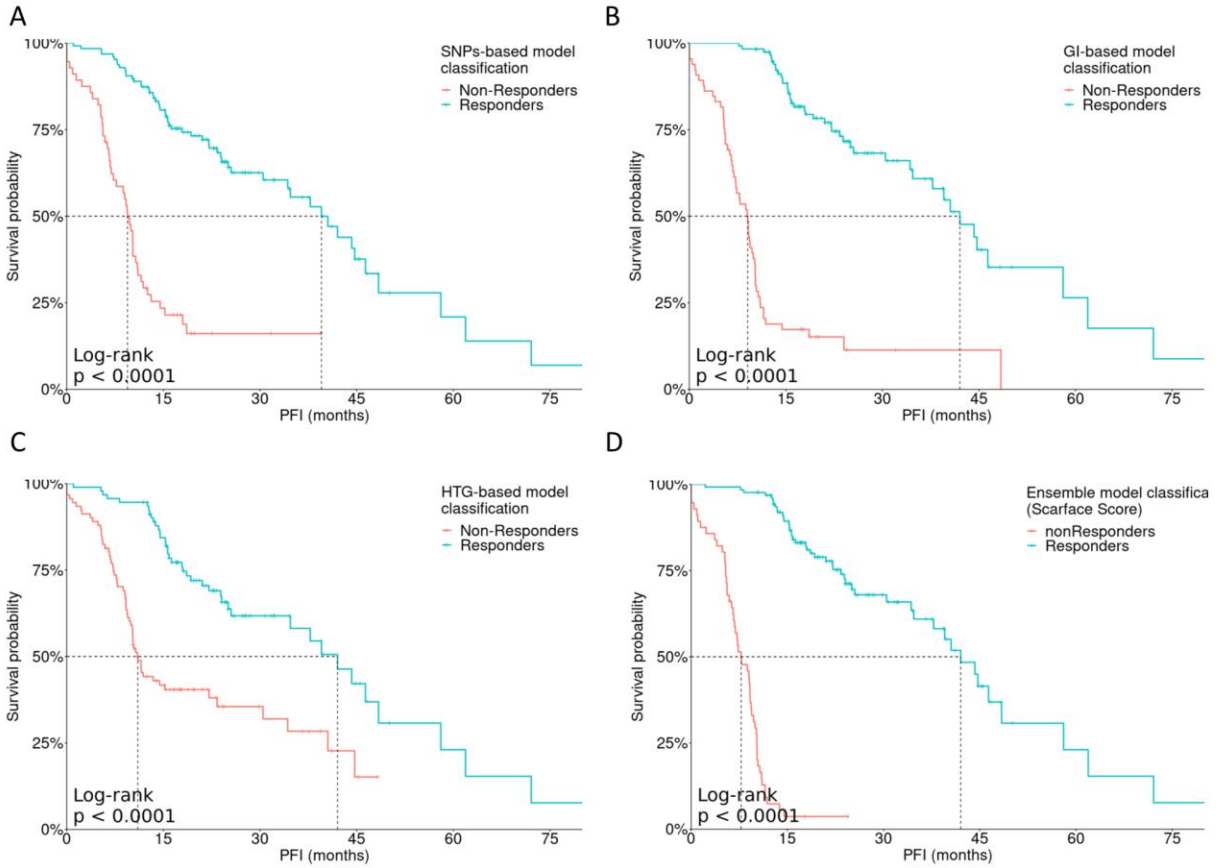
DistrIbution of genetic alterations of DNA repair genes

	Accuracy (95 % CI)	Sensitivity; Specificity	Kappa
SNPs Model	0.8077 (0.6747-0.9037)	0.7222; 0.8529	0.5752
GI Model	0.8077 (0.6747-0.9037)	0.9444; 0.7353	0.6154
HTG Model	0.8909 (0.7775-0.9589)	0.8750; 0.8974	0.7450
Ensemble Model	0.9615 (0.8679-0.9953)	0.8889; 1.0000	0.9128

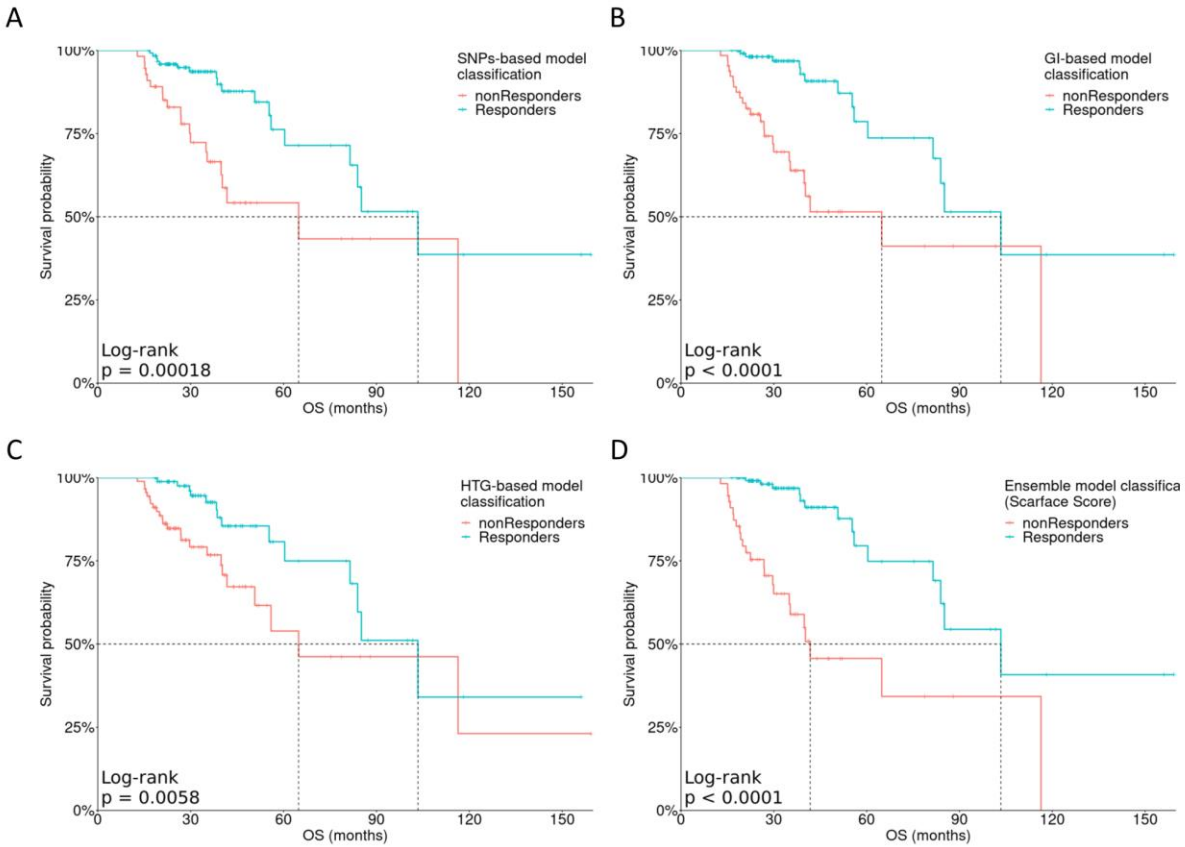
ROC curves for different predictive models (PFI 12 months)



KM curves for Platinum-Free Interval (PFI) of the different predictive models

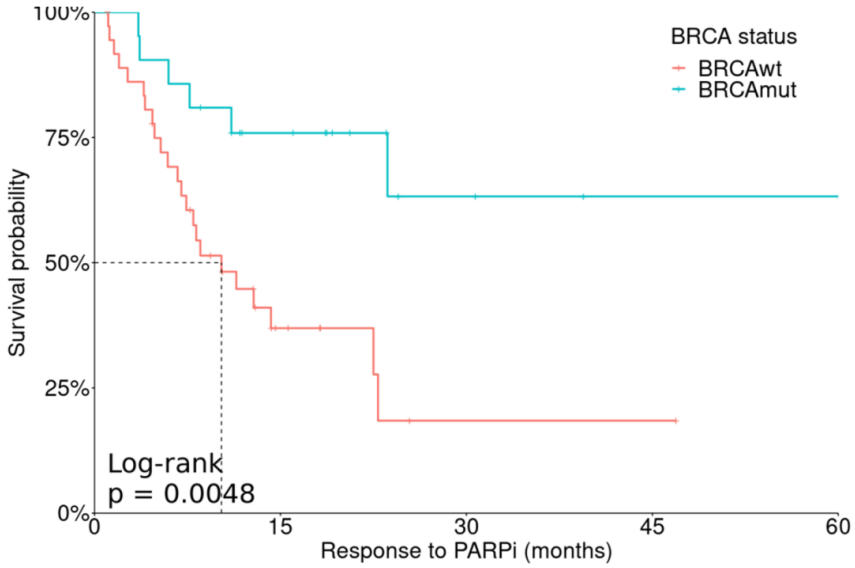


KM curves for Overall Survival (OS) for different predictive models

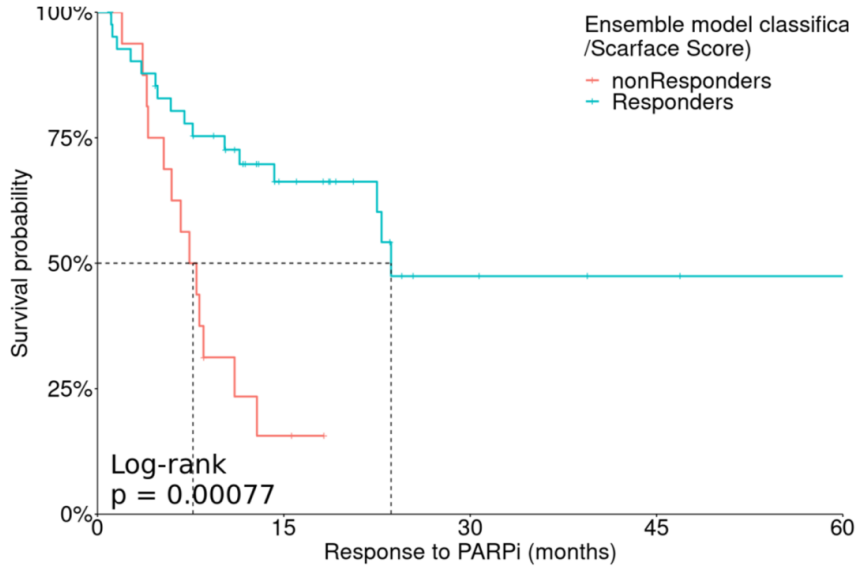


KM curves with PARPi response for *BRCA* status and Ensemble model prediction

A



B



- Data annotation is crucial for a successful precision medicine using AI tools.
- AI tools from tumor profiling are very useful to answer specific clinical questions.
- MPD and AIMS algorithms from HTG BC profiles provides a very accurate recurrence-risk and molecular subtyping classification.
- SCARFACE score identifies ovarian cancer patients that may benefit from platinum-based and PARPi therapies.

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