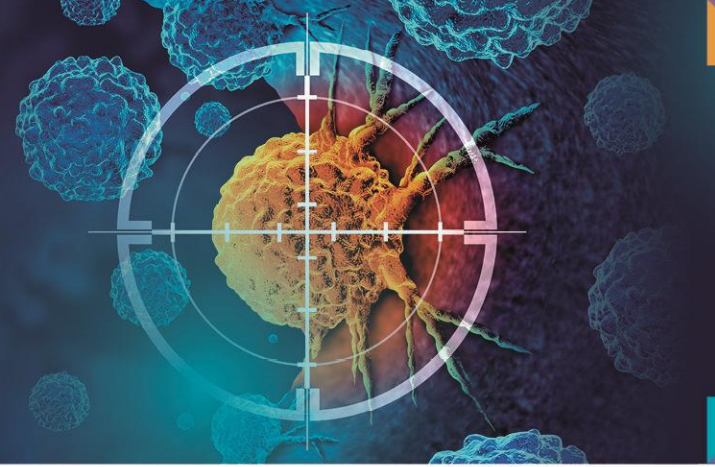
XVIII SIMPOSIUM

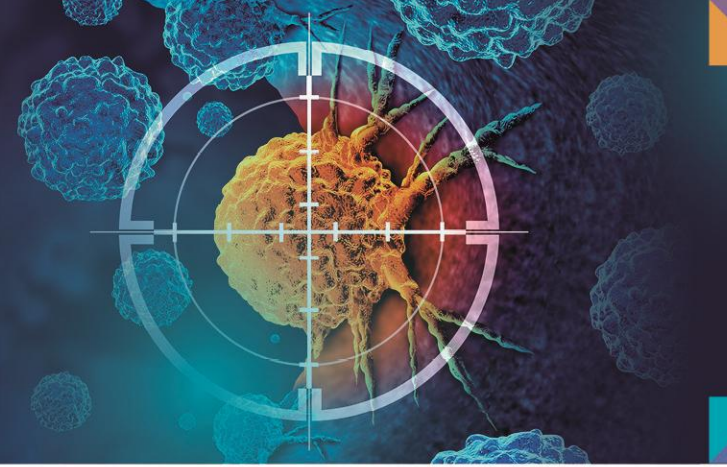
BASES BIOLÓGICAS DEL CÁNCER E INNOVACIÓN TERAPÉUTICA

MÁS DE 20 AÑOS A LA VANGUARDIA DE LA FORMACIÓN EN LA BIOLOGÍA Y TRATAMIENTO DEL CÁNCER



¿Qué debe demostrar un biomarcador para cambiar la práctica clínica?

Enrique Lastra
Servicio de Oncología Médica
Hospital Universitario de Burgos



… utilidad clínica

GUIÓN

- Conceptos:
  - Biomarcador, Tumor Biomarker Test (TBT), AI-based Biomarker
- Descubrimiento biomarcador
- Evidencia científica biomarcador/Validación TBT
- Validación AI-based Biomarker
- Implementación
- Conclusión

CONCEPTOS

- **Biomarcador:**
  - Característica
  - Medida objetivamente
  - Evaluada como indicador de proceso biológico normal
  - Indicador de procesos patológicos
  - Indicador respuesta biológica una exposición, intervención
  - Indicador respuesta biológica a intervención terapéutica

Clinical Pharmacology and Therapeutics. 2001; 69(3): 89-94.

Ou F-S. Journal of Thoracic Oncology. 2021; 16(4): 537-545

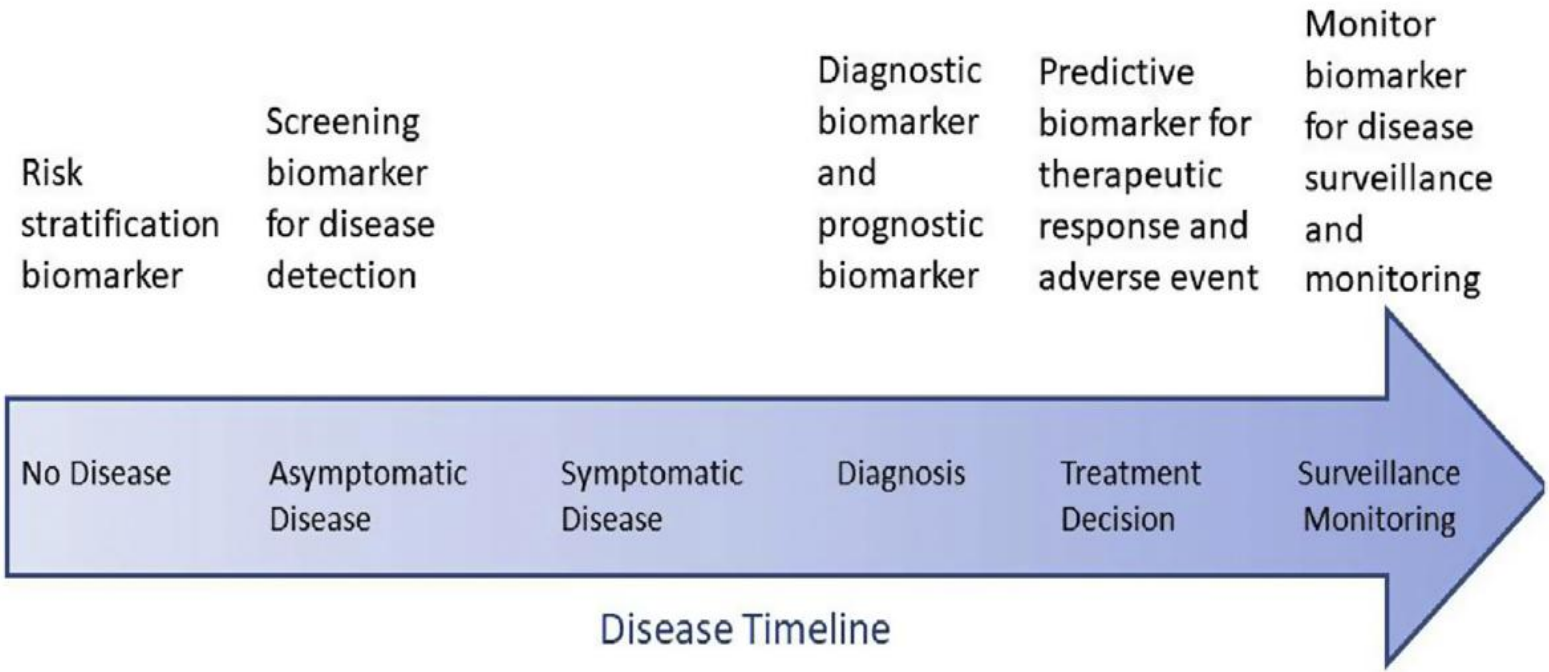


Figure 1. Use of biomarkers in relation to the course of disease.

Ou F-S Journal of Thoracic Oncology. 2021; 16(4): 537-545

- **Biomarcador:**
  - Moléculas biológicas relacionadas con cáncer
  - Proteínas, alteraciones genómicas, alteraciones celulares
  - Requisitos:
    - Binaria/contínua (cuantificable, límites significación)
    - Detectable en muestras accesibles
    - Dispositivo para generar resultado
    - Tiempo de retorno rápido

Ou F-S. Journal of Thoracic Oncology. 2021; 16(4): 537-545

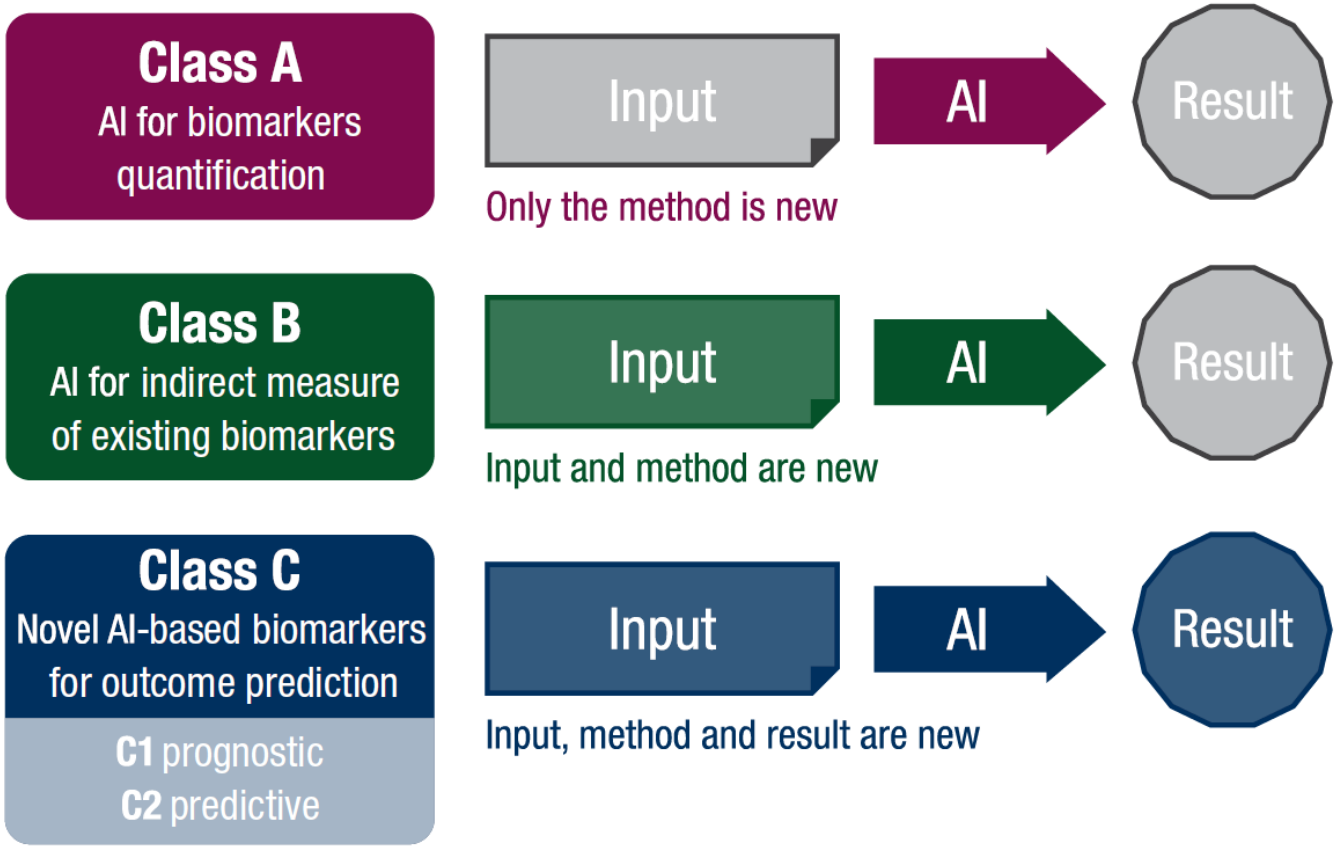
- **Tumor Biomarker Test:**
  - Dispositivo/herramienta/instrumento que analiza uno o varios biomarcadores relacionados con cáncer, técnicas de laboratorio



Hayes DF. J Clin Oncol. 2020; 39: 238-248

- **AI-based Biomarker:**
  - "Señal" en una medición biológica
    - Firma genómica, patrón morfológico celular, patrón radiológico
  - Medición no siempre en tejido
  - AI: Análisis complejo múltiples datos imperceptibles
  - Transformación de datos en conocimiento clínico
    - Predicción diagnóstica, pronóstica, terapéutica, evolutiva

Aldea M. Annals of Oncology. 2026; 37(3): 414-25



Aldea M. Annals of Oncology. 2026; 37(3): 414-25

DESCUBRIMIENTO

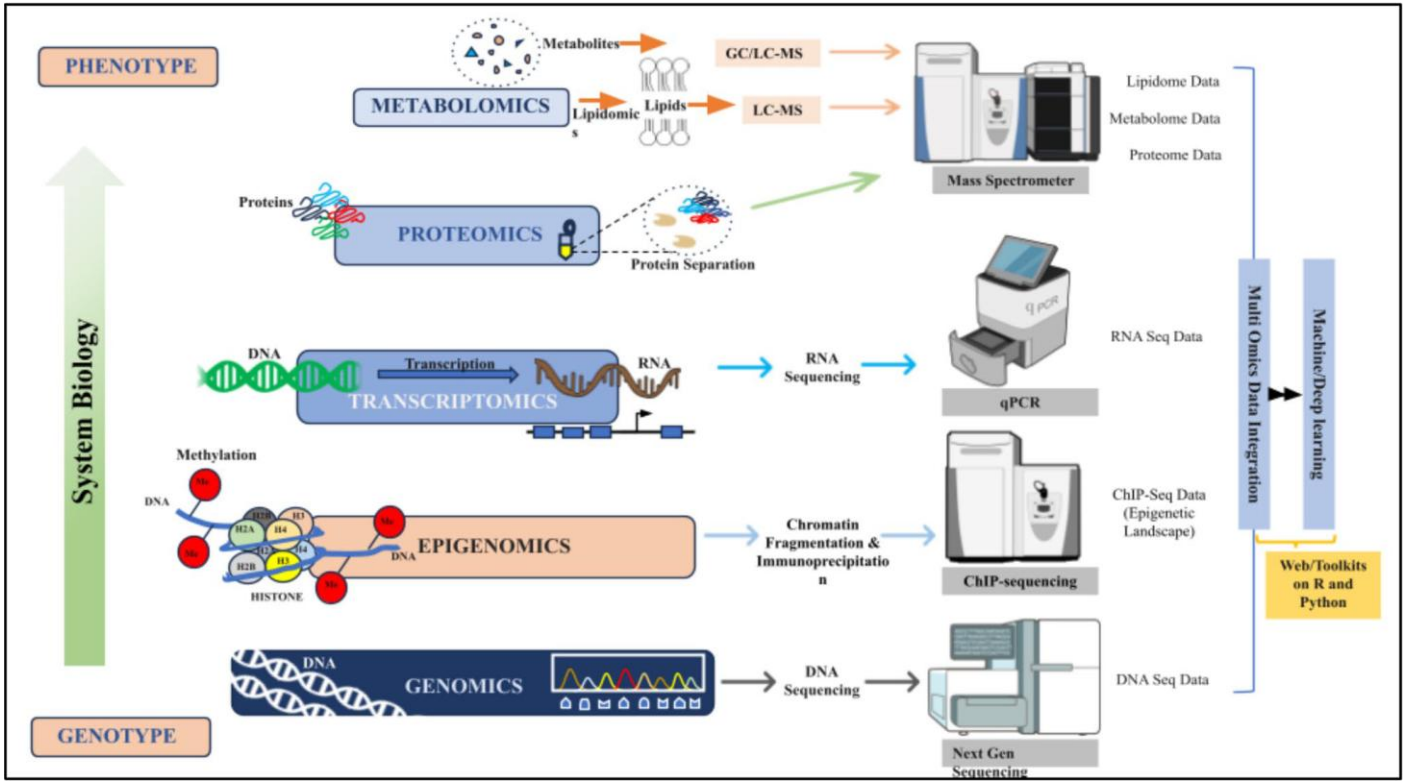
- Investigación básica, omic, traslacional, preclínica



  - “Proof of Concept”
  - Puede no captar complejidad del cáncer, dinamismo marcador

Clinical Pharmacology and Therapeutics. 2001; 69(3): 89-94.

Tamborero D. Nature, 2022; 3: 251-261



ARTIFICIAL INTELLIGENCE
APPLIED TO:

ELECTRONIC HEALTH RECORDS
RADIOMICS
MICROBIOME
EXPOSOME
DIGITAL PATHOLOGY
"PATHOMIC"
THERAGNOSIS

"BLACK BOX"

Biswas S. Clinical and Translational Oncology. 2026; 28:5117-5142

SCORE MULTIDATA PARA CLASIFICAR POBLACIÓN DE RIESGO

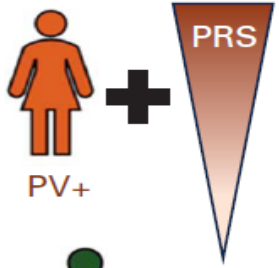
+ ARTIFICIAL INTELLIGENCE
APPLIED TO:

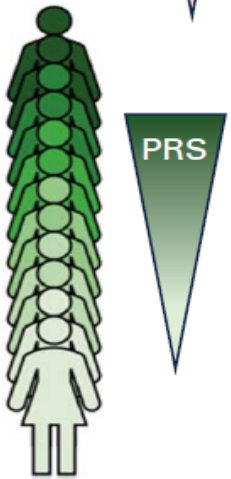
Genomics, epigenomics, transcriptomics | **Proteomics, metabolomics**

ELECTRONIC HEALTH RECORDS
RADIOMICS, MICROBIOMA, EXPOSOMA
DIGITAL PATHOLOGY OF BIOSPECIMENS



Unaffected individuals undergo whole-genome evaluation for
Rare risk variants
PRS

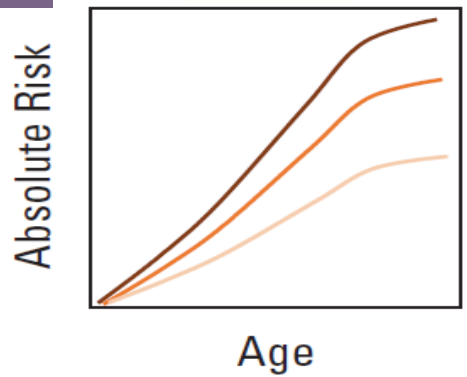


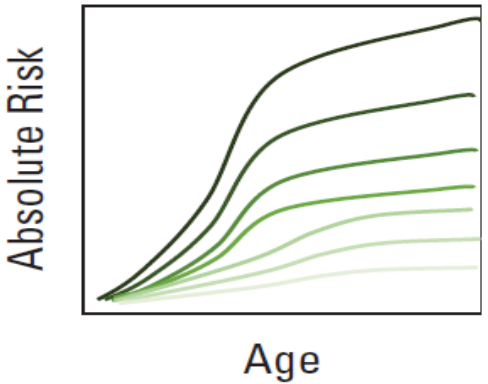


- Family history
- Age
- Genetic ancestry
- Self-identified race
- BMI
- Lifestyle factors
- Reproductive factors
- Biopsy history
- Breast density
- Medical history

Risk stratification biomarker

No Disease





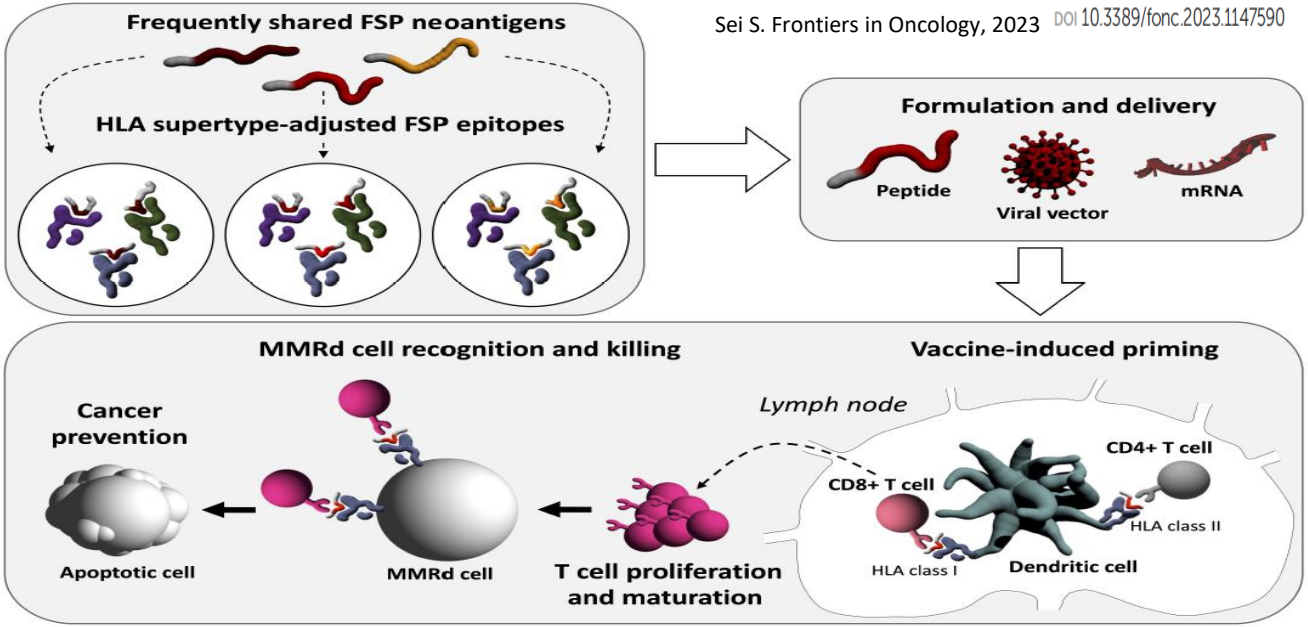
Maxwell KN. Journal of Clinical Oncology. 2024, 42: 1462-1465

PREVENCIÓN PRIMARIA
INMUNOPREVENCIÓN
SÍNDROME DE LYNCH

No Disease

ISRCTN78380445 https://doi.org/10.1186/ISRCTN78380445

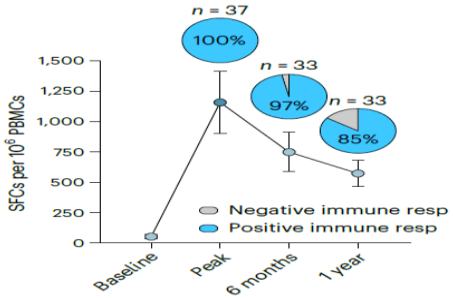
A clinical trial testing a new treatment called mRNA-4194 for people with Lynch syndrome

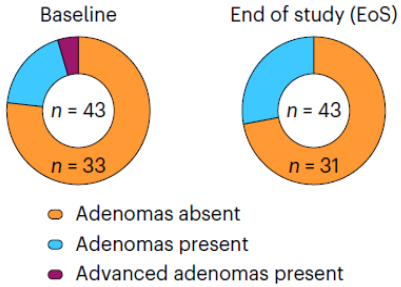


Sei S. Frontiers in Oncology, 2023 DOI 10.3389/fonc.2023.1147590

Nous-209 neoantigen vaccine for cancer prevention in Lynch syndrome carriers: a phase 1b/2 trial

D´Alise AM. Nature Medicine. 2026, 32:1002-11



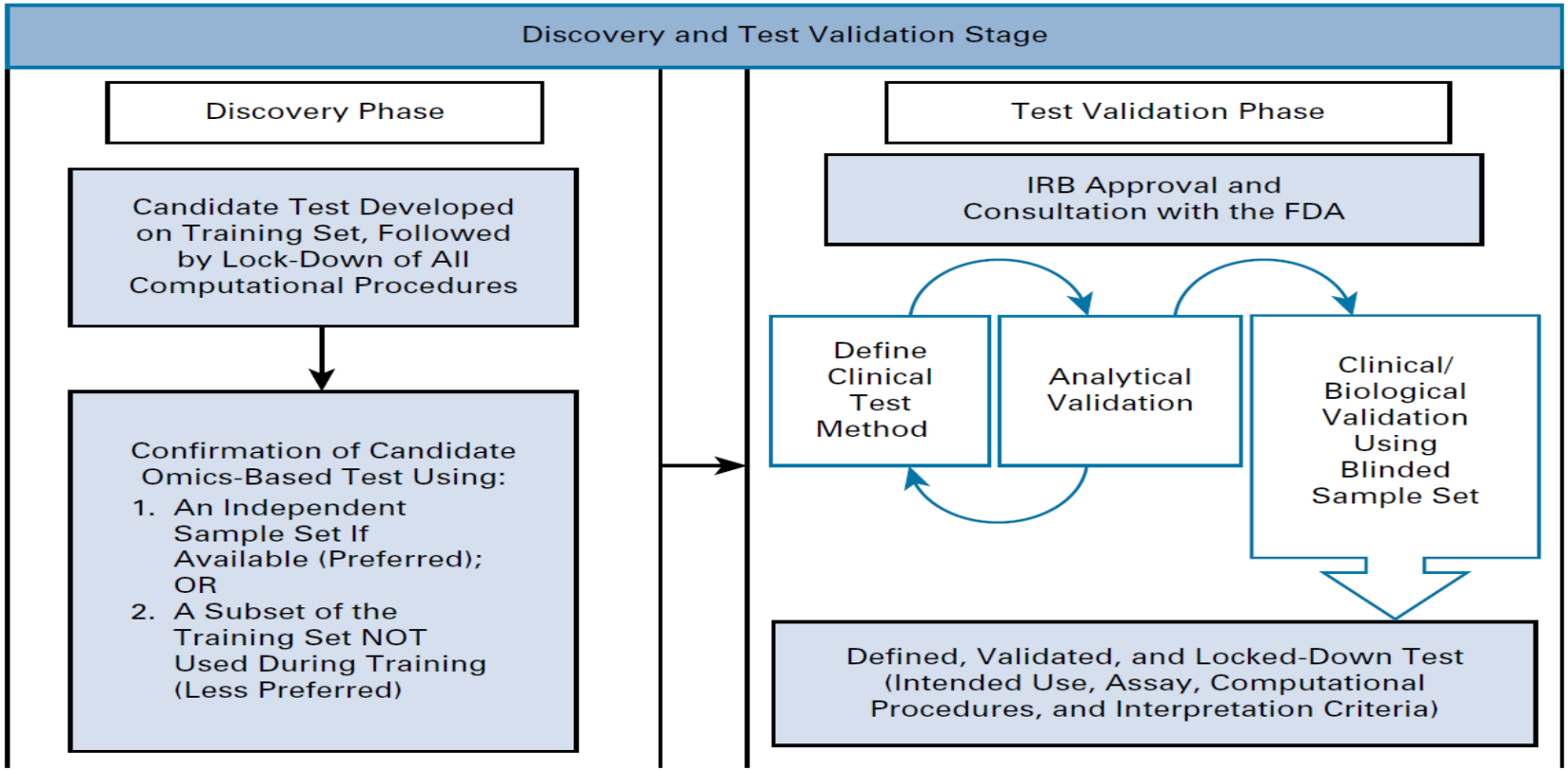


EVIDENCIA CIENTÍFICA BIOMARCADOR/VALIDACIÓN TBT

Biomarker Discovery

- Aims to identify a potential biomarker using available specimens
- Randomization and blinding can be used to avoid bias
- Use appropriate analysis method and control for multiple testing
- Consider the level of evidence

Ou F-S. Journal of Thoracic Oncology. 2021; 16(4): 537-545



Hayes DF. J Clin Oncol. 2020; 39: 238-248

VALIDACIÓN ANALÍTICA

Pre-analytical	Issues regarding collection, handling, transport, processing, and storage of a specimen that may affect the subsequent analysis.
Analytical validity	Ability of an assay to detect and measure, with statistical significance, the presence of a biomarker of interest accurately, reproducibly, and reliably.

Analytical Validation

- Aims to establish the performance characteristics of the biomarker
- Internal validation and external validation are both appropriate

Table 1. Metrics Useful for Evaluating Biomarker Performance

Metrics	Description
Sensitivity	The proportion of cases that test positive
Specificity	The proportion of controls that test negative
Positive predictive value	Proportion of test-positive patients who actually have the disease; is a function of disease prevalence
Negative predictive value	Proportion of test-negative patients who truly do not have the disease; is a function of disease prevalence
ROC curve	Plot of sensitivity (true positive rate) versus 1 specificity (false-positive rate), with a data point calculated for every value of the marker in the data set
Discrimination	How well the marker distinguishes cases from controls; often measured by the area under the ROC curve; ranges from 0 to 1, with 0.5 indicating performance equivalent to a coin flip and 1 corresponds to perfect ability to distinguish
Calibration	How well a marker estimates the risk of disease or of the event of interest

Ou F-S Journal of Thoracic Oncology. 2021; 16(4): 537-545

Merker JD. J Clin Oncol. 2018; 36: 1631-1641

VALIDACIÓN CLÍNICA

Clinical validity	Ability of an assay to divide, with statistical significance, one population into two or more groups on the basis of outcomes, such as presence of cancer or treatment response.

Clinical Validation
- External validation is the appropriate approach
- Demonstrate “clinical validity”
  - To establish an association between the biomarker and the endpoint of interest

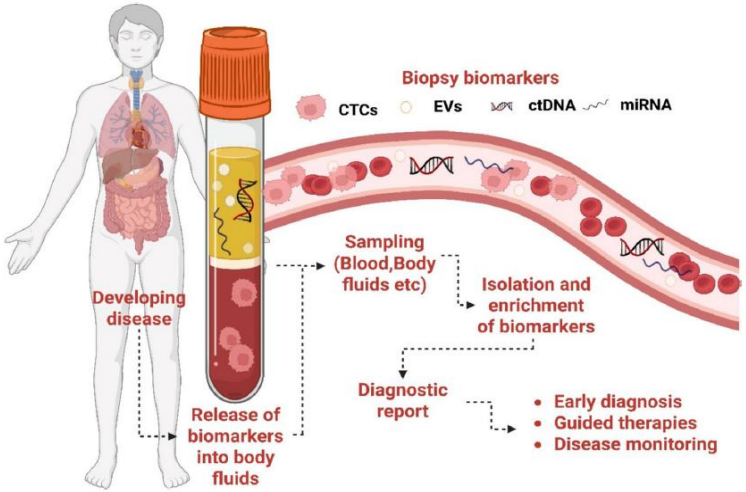
Ou F-S Journal of Thoracic Oncology. 2021; 16(4): 537-545

Merker JD. J Clin Oncol. 2018; 36: 1631-1641

PREVENCIÓN SECUNDARIA
BIOPSIA LÍQUIDA

Screening biomarker for disease detection

Asymptomatic Disease

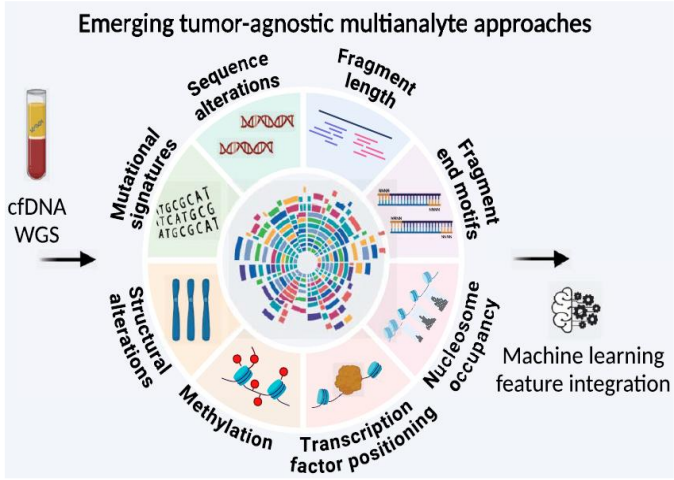


Dhiman VK. Clinical and Translational Oncology. 2026 (28):4469-90

GRAIL Sasieni P. Nature Medicine. 2026: 3770-80

Cancer detection rate[c], % (*n*/*N*) (95% CI)	0.60 (419/70,325) (0.54–0.66)
Number needed to screen[d], *n* (95% CI)	168 (153–185)
PPV, % (*n*/*N*) (95% CI)	58.0 (419/722) (54.4–61.6)
NPV, % (*n*/*N*) (95% CI)	98.98 (68,895/69,603) (98.91–99.05)
Specificity, % (*n*/*N*) (95% CI)	99.56 (68,895/69,198) (99.51–99.61)

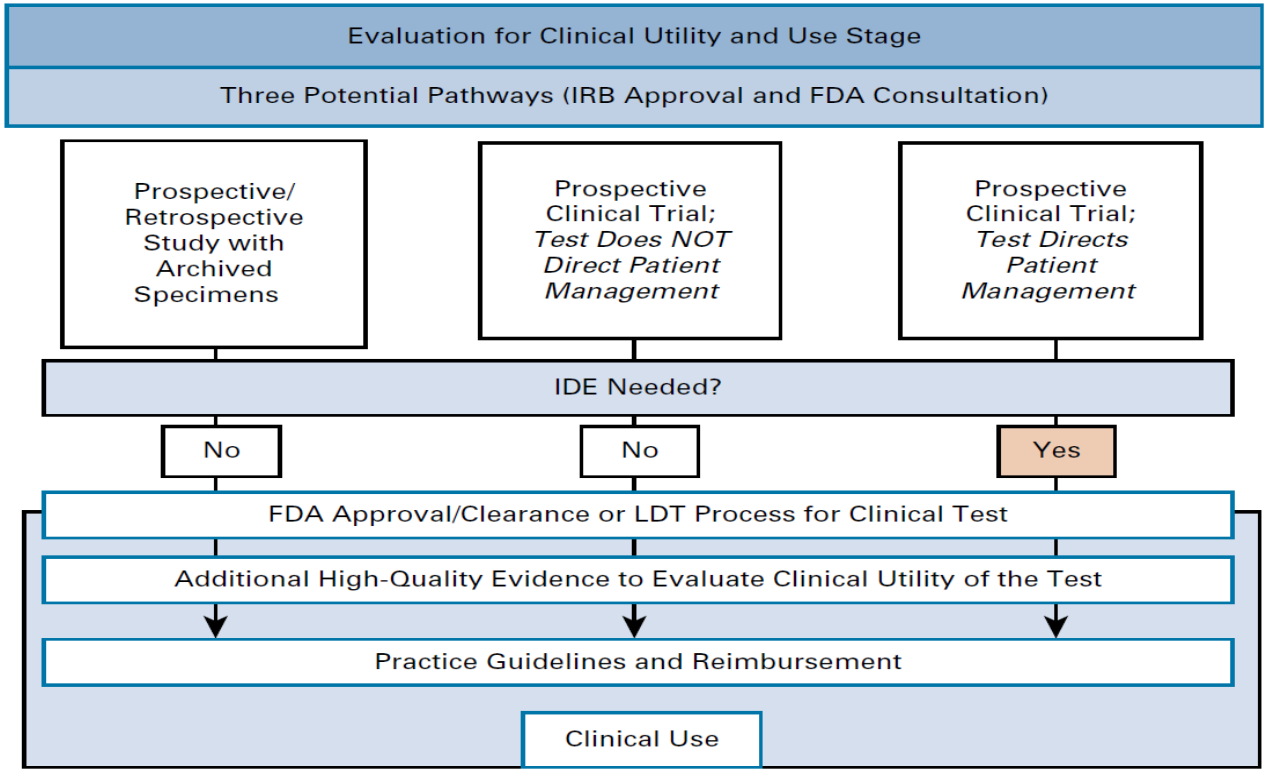
Aredo JC. ASCO Educational Book. 2025



MCED cancer detection rate, % (95% CI) (TP/*N*)	0.54% (0.47–0.63%)
PPV, % (95% CI) (TP/(TP+FP))	60.3% (54.5–65.8%)
NPV, % (95% CI) (TN/(FN+TN))	99.2% (99.1–99.3%)
12-month episode sensitivity, % (95% CI) (TP/(TP+FN))	
All cancer types	39.3% (34.9–44.0%)
Prespecified subgroup of 12 cancers responsible for two-thirds of US cancer deaths[b]	69.8% (62.8–76.0%)
Prespecified subgroup of six aggressive cancers with low 5-year survival[c]	66.2% (55.1–75.8%)
Specificity, % (95% CI) (TN/(FP+TN))	99.64% (99.57–99.70%)

PATHFINDER 2. Nabavizadeh N. Nature Medicine. 2026: 3760-9

VALIDACIÓN UTILIDAD CLÍNICA



Hayes DF. J Clin Oncol. 2020; 39: 238-248

TABLE 1. Distinction of Clinical Utility from Clinical Validity for a TBT

Elements Necessary to Demonstrate that a TBT with Clinical Validity Has Clinical Utility
Preanalytical issues[36]
Must be tightly controlled (see specimen collection below)
Analytical issues[37]
Assay locked down before study conducted
Cut point or provision of continuous variable risk categories determined before study conducted
Source of specimens/data (level of evidence 1)[14]
Prospective clinical trial specifically addressing clinical utility for the intended use of the TBT
Or
Prospective-retrospective studies from 2 or more previously conducted prospective clinical trials in which:
The intended use of the TBT can be determined
Data are prospectively collected with clinical trial quality measures
Specimens are prospectively collected and stored in a manner suitable for assay performance
Similar if not identical results are obtained

Hayes DF. J Clin Oncol. 2020; 39: 238-248

Clinical utility	Ability to demonstrate, with statistical significance, improvement in the diagnosis, treatment, management, or prevention of cancer, with the use of the assay compared with not using the assay.

- Demonstrate “clinical utility”
  - To establish the clinical usefulness of a marker, i.e., whether use of the marker in clinical care actually results in improved patient outcomes
- Retrospective use of prospectively collected specimens, e.g. the PRoBE design, is appropriate for validating diagnostic, screening, and prognostic biomarkers
- Many prospective clinical trial design options are available for validating predictive biomarkers

Ou F-S Journal of Thoracic Oncology. 2021; 16(4): 537-545

Merker JD. J Clin Oncol. 2018; 36: 1631-1641

Sarcoma histologies with associated chromosomal translocations

Translocation	Genes	Type of fusion gene
Ewing sarcoma (OMIM#133450)		
t(11;22)(q24;q12)	*EWSR1::FLI1*	Transcription factor
t(21;22)(q22;q12)	*EWSR1::ERG*	Transcription factor
t(7;22)(p22;q12)	*EWSR1::ETV1*	Transcription factor
t(17;22)(q12;q12)	*EWSR1::ETV4*	Transcription factor
t(2;22)(q35;q12)	*EWSR1::FEV*	Transcription factor
t(2;16)(q35;p11)	*FUS::FEV*	Transcription factor
t(16;21)(p11;q24)	*FUS::ERG*	Transcription factor
Undifferentiated round cell sarcoma with *BCOR*- or *CIC*-rearrangements[1] (OMIM#300485, #612082, #606009)		
t(X;X)(p11;p11)	*BCOR::CCNB3*	Cell cycle progression
t(4;19)(q35;q13) or t(10;19)(q26;q13)[1]	*CIC::DUX4*	Transcription factor
Clear cell sarcoma (OMIM#123803)		
t(12;22)(q13;q12)	*EWSR1::ATF1*	Transcription factor
Desmoplastic small round cell tumor of the abdomen (OMIM#133450)		
t(11;22)(p13;q12)	*EWSR1::WT1*	Transcription factor
Extraskeletal myxoid chondrosarcoma (OMIM#600542)		
t(9;22)(q22-31;q11-12)	*EWSR1::NR4A3*	Transcription factor
Myxoid liposarcoma (OMIM#126337, #137070)		
t(12;16)(q13;p11)	*FUS::DDIT3* (*FUS::CHOP*)	Transcription factor
t(12;22)(q13;q12)	*EWSR1::CHOP* (*EWSR1::DDIT3*)	Transcription factor
Alveolar rhabdomyosarcoma (OMIM#268220)		
t(2;13)(q35;q14)	*PAX3::FOXO1A**	Transcription factor
t(1;13)(p36;q14)	*PAX7::FOXO1A**	Transcription factor
Congenital infantile spindle cell rhabdomyosarcoma		
t(6;6)(q24.1;q22.1)	*VGLL2::CITED2*	Transcription factor
t(6;8)(q22.1;q13.3)	*VGLL2::NCOA2*	Transcription factor
t(11;8)(p15.3;q13.3)	*TEAD1::NCOA2*	Transcription factor
t(2;8)(q36;q13.3)	*PAX3::NCOA2*	Transcription factor
t(6;8)(p21.1;q13.3)	*SRF::NCOA2*	Transcription factor
Synovial sarcoma (OMIM#312820)		
t(X;18)(p11;q11)	*SS18::SSX1*, *SSX2*, or *SSX4*	Remodels chromatin to alter transcription
Dermatofibrosarcoma protuberans (OMIM#607907)		
t(17;22)(q22;q13)	*COL1A1::PDGFB*	Growth factor
Congenital fibrosarcoma (OMIM#191316)		
t(12;15)(p13;q25)	*ETV6::NTRK3*	Transcription factor receptor
Inflammatory myofibroblastic tumor		
2p23 rearrangements	*TMP3::ALK*	Growth factor receptor
	TMP4::ALK	Growth factor receptor
Alveolar soft part sarcoma (OMIM#606243)		
t(X;17)(p11.2;q25)	*ASPL::TFE3*	Transcription factor
Solitary fibrous tumor (OMIM#602381)		
Inversion 12q13	*NAB2::STAT6*	Transcription factor
Epithelioid hemangioendothelioma		
t(1;3)(p36;q25)	*WWTR1::CAMTA1*	Transcription factor

Note that for some tumors, notably Ewing sarcoma, multiple variant translocations have been observed involving related genes.

OMIM: Online Mendelian Inheritance in Man, available at http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim.

* *FOXO1A* gene, also known as the *FKHR* gene.

Reference:
1. Pappo AS, Dirksen U. Rhabdomyosarcoma, Ewing sarcoma, and other round cell sarcomas. J Clin Oncol 2015; 33:3085.

Adapted with permission from: Helman LJ, Meltzer P. Mechanisms of sarcoma development. Nature Reviews: Cancer 2003; 3:685. Copyright © 2003 MacMillan Publishers Ltd.

UpToDate®

Diagnostic biomarker and prognostic biomarker

Diagnosis

Clinical effect of molecular methods in sarcoma diagnosis (GENSARC): a prospective, multicentre, observational study

Added value of this study

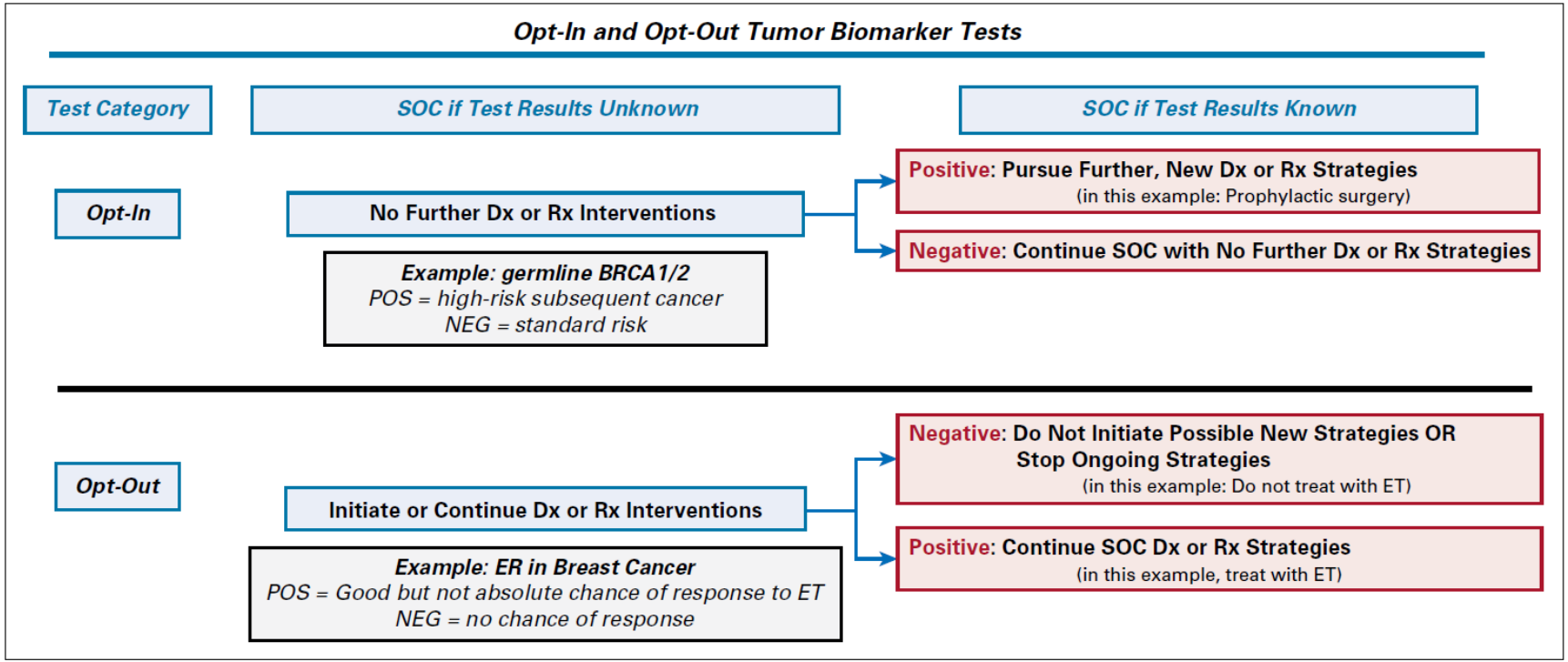
Here, we report that the systematic use of molecular tests allows diagnosis refinement in up to 53 (13%) of 384 cases, even by a pathologist who is an expert in the specialty. In all the cases, diagnosis refinement had an effect on either treatment strategy, prognosis assessment, or both.

Implications of all the available evidence

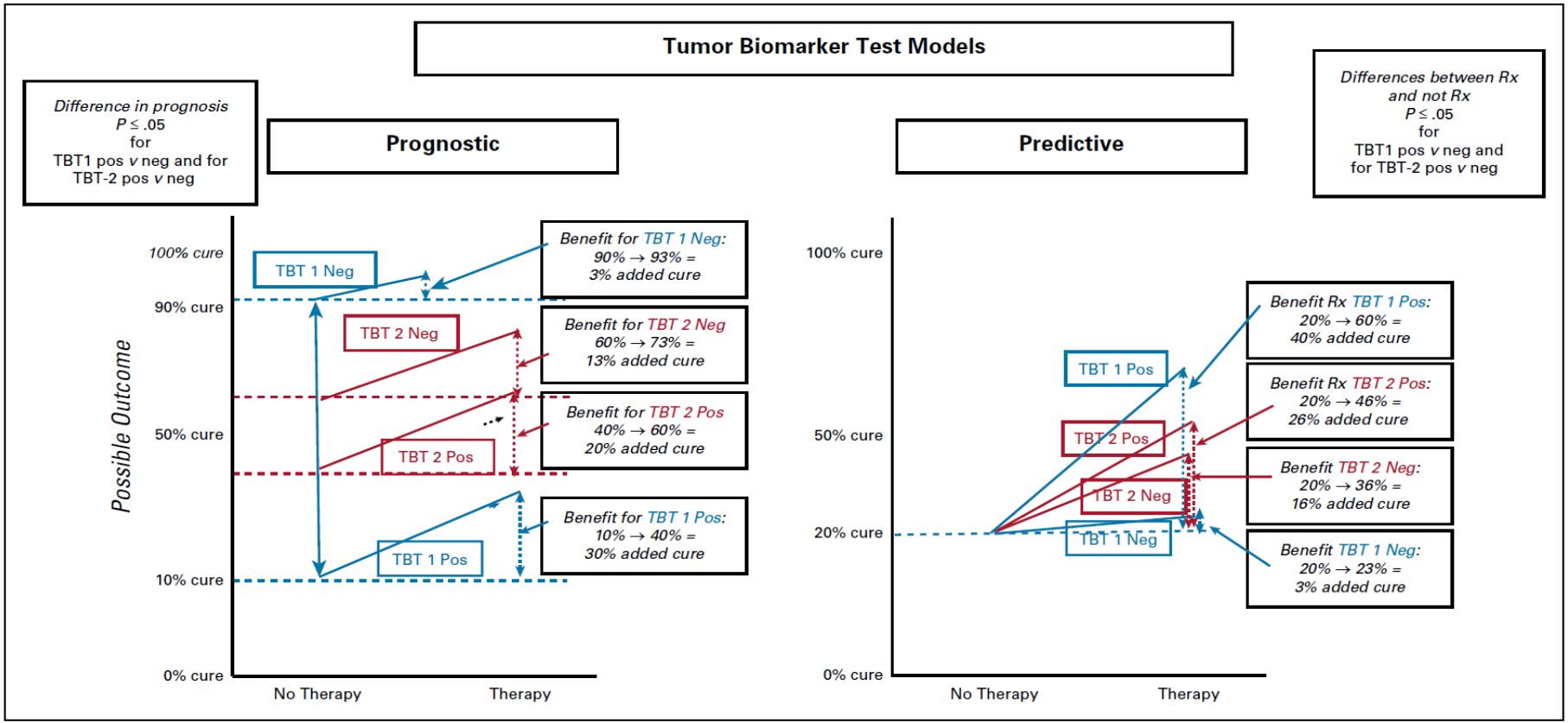
For all sarcoma with recurrent genetic aberrations, molecular diagnosis test must be done even when the diagnosis is regarded as certain by the sarcoma-expert pathologist.

Italiano A. Lancet Oncol. 2016; 17: 532-38

Copyrights apply



Hayes DF. J Clin Oncol. 2020; 39: 238-248



MCID: Minimal Clinical Important Difference

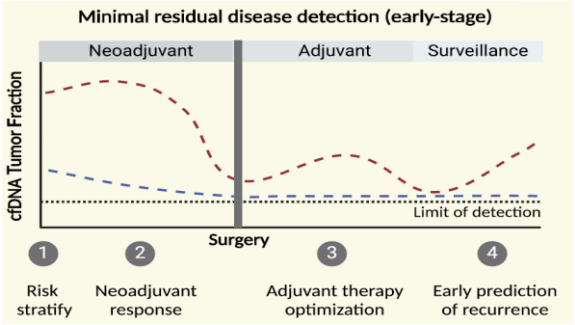
Hayes DF. J Clin Oncol. 2020; 39: 238-248

UTILIDAD CLÍNICA PRONÓSTICO RECIDIVA: PREVENCIÓN TERCIARIA

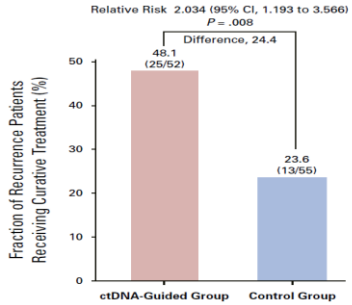
Diagnostic biomarker and prognostic biomarker

Diagnosis

Aredo JC. ASCO Educational Book. 2025



ctDNA Methylation-Guided Surveillance in CRC



Tie J. Nat Med. 2025, 31(5):1509-18

Circulating tumor DNA analysis guiding adjuvant therapy in stage II colon cancer: 5-year outcomes of the randomized DYNAMIC trial

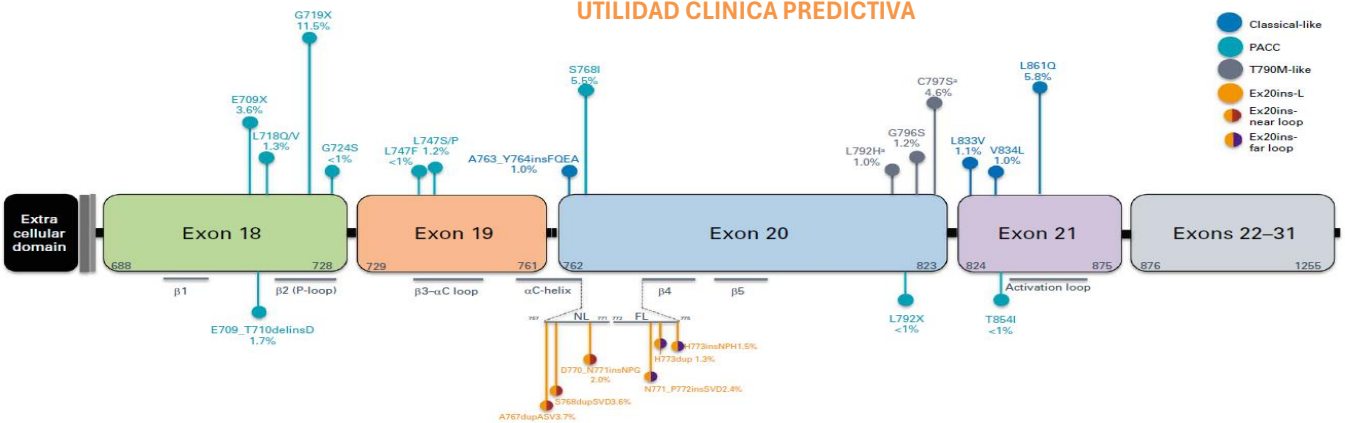
Reducción en el uso de quimioterapia: 15% (ctDNA) vs 28% (no ctDNA)

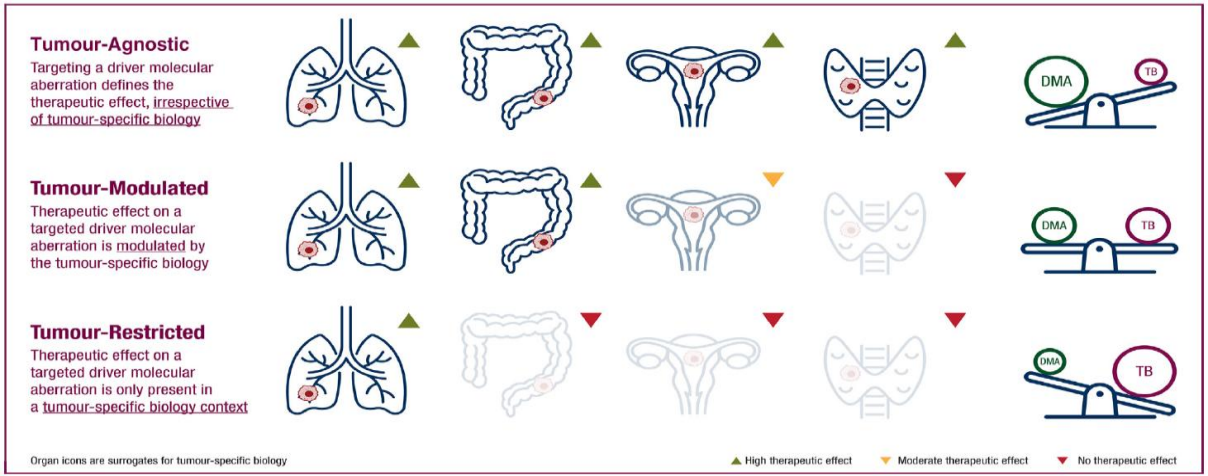
Population	No. of Patients	5-year RFI	5-year RFS	5-year DSS	5-year OS
Overall					
Standard management	147	89.8%	87.2%	97.2%	93.3%
ctDNA-guided	294	91.7%	88.3%	97.9%	93.8%
		HR 1.16 (0.60, 2.25) *P* = 0.65	HR 1.01 (0.56, 1.81) *P* = 0.93	HR 1.19 (0.35, 4.09) *P* = 0.79	HR 1.05 (0.47, 2.37) *P* = 0.887

Dynamic Circulating Tumor DNA Methylation Monitoring Guiding Postoperative Surveillance in Nonmetastatic Colorectal Cancer: A Prospective, Randomized, Phase III FIND Trial

Mo S. Journal of Clinical Oncology. 2026. DOI https://doi.org/10.1200/JCO-25-03009

UTILIDAD CLÍNICA PREDICTIVA





The way we name cancers needs to change

Atomización Molecular:
"Outliers"
"Cazando unicornios"

ETAC-Taxonomy

ESMO
Tumor Agnostic Classifier

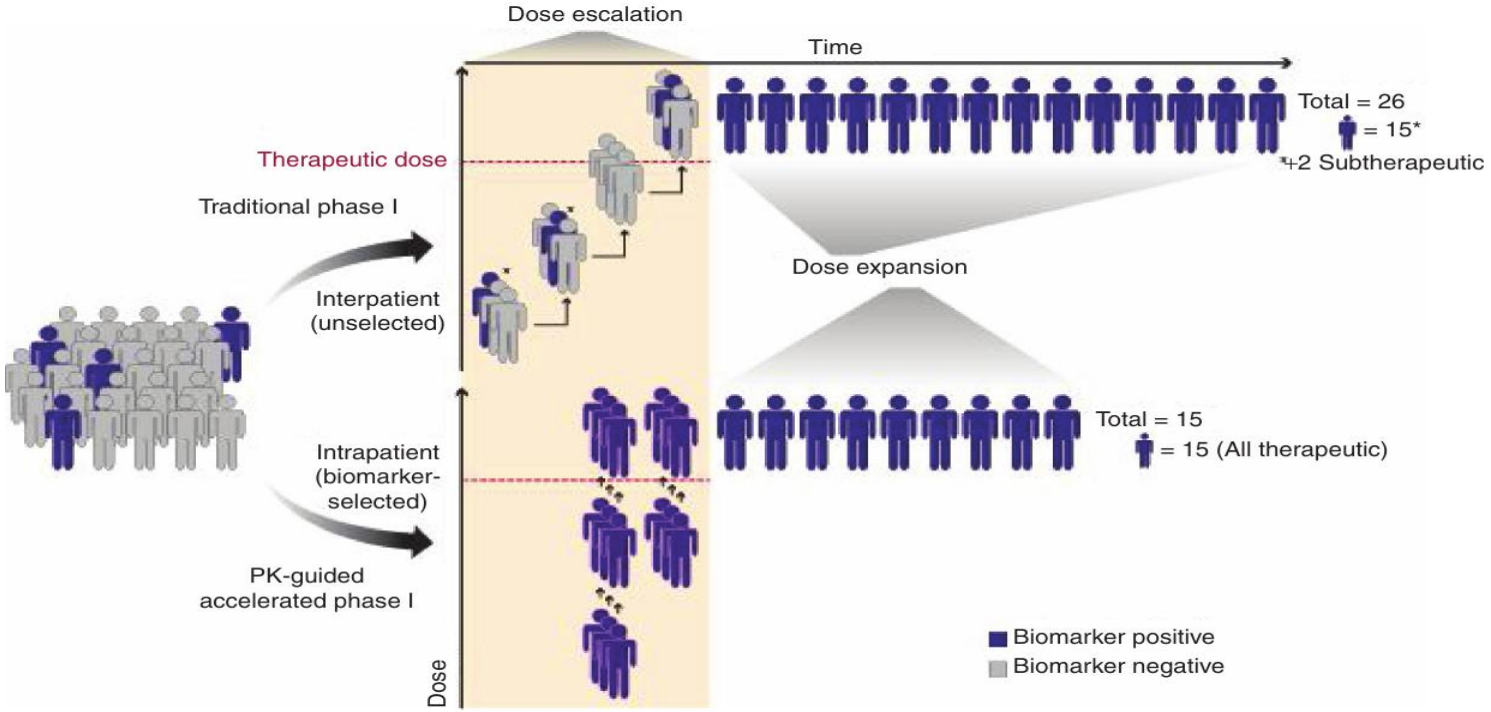
André F. Nature. 2024 (626): 26-9

Monaca F. Journal of Clinical Oncology. 2026

Wang VE. JAMA Oncology. 2024, 10(1):52-3

Westphalen CB. Annals of Oncology. 2024; 35(11): 936-53

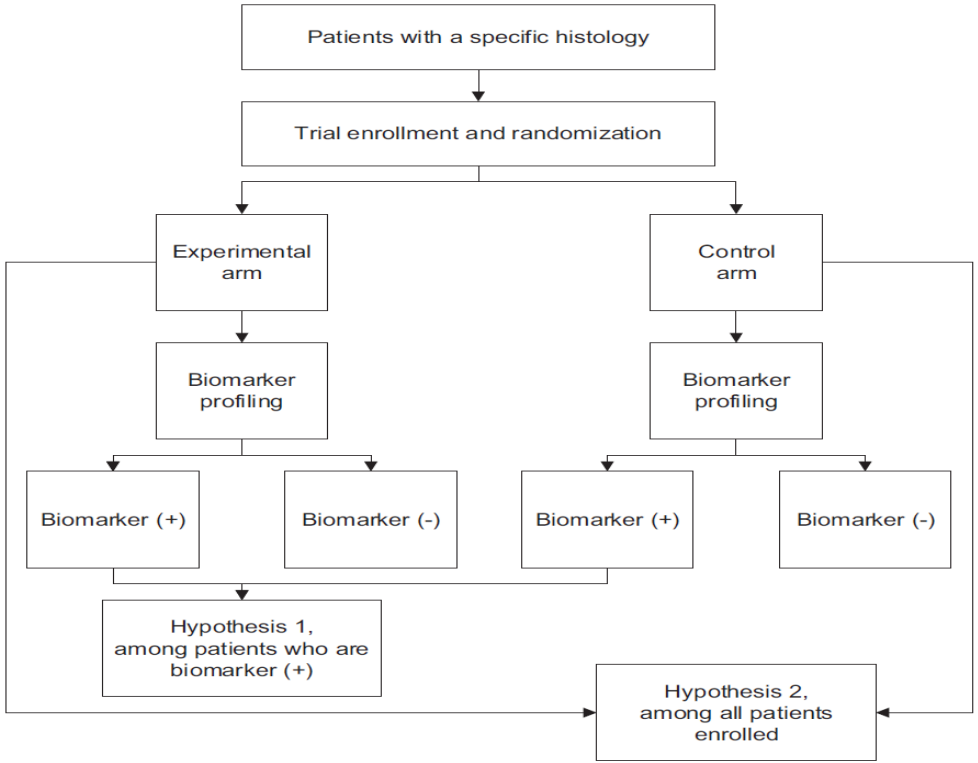
UTILIDAD CLÍNICA PREDICTIVA: ESTUDIOS PROSPECTIVOS



Dosis de eficacia máxima tolerable: Fase I-II, selección molecular, farmacocinética, farmacodinámica

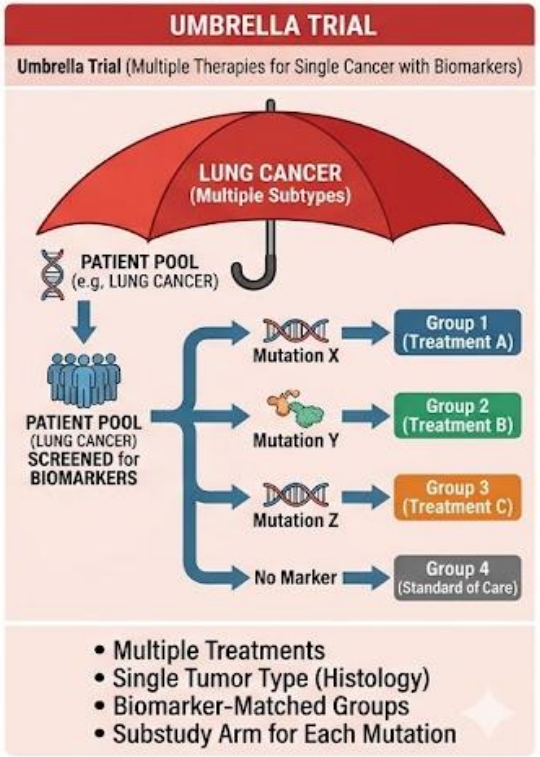
Drilon A. Cancer Discov. 2017; 7(9): 963-972

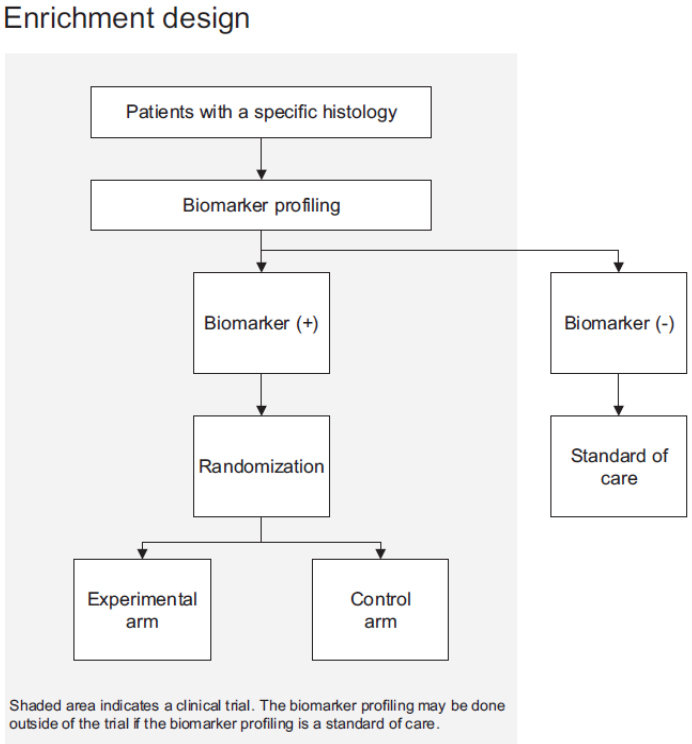
Subgroup design



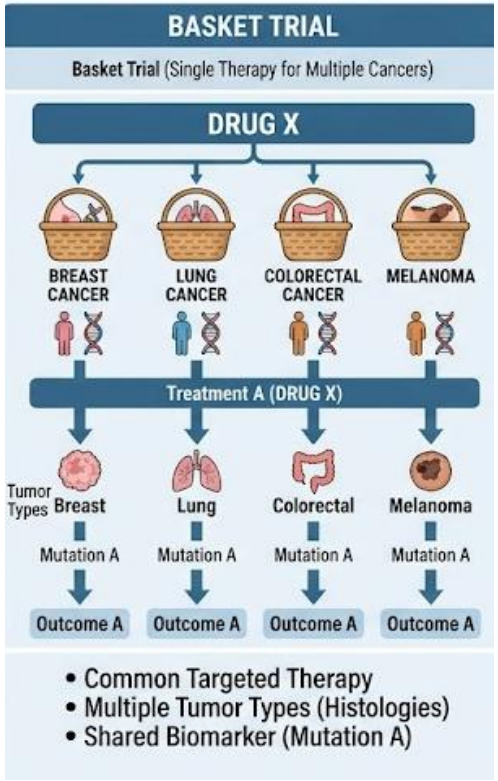
Ou F-S Journal of Thoracic Oncology. 2021; 16(4): 537-545

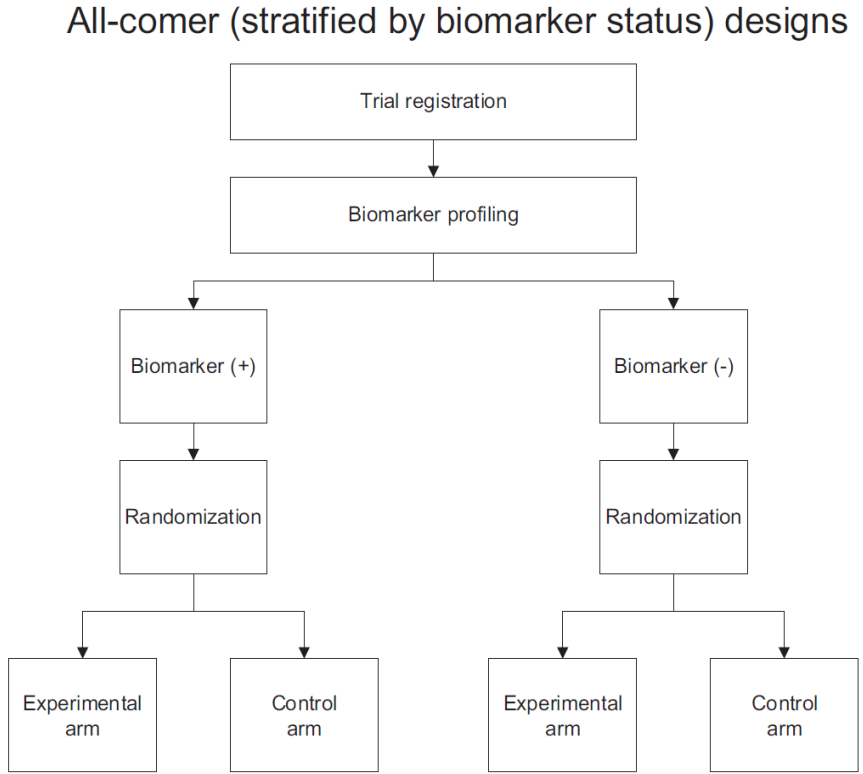
UTILIDAD CLÍNICA PREDICTIVA: ESTUDIOS PROSPECTIVOS





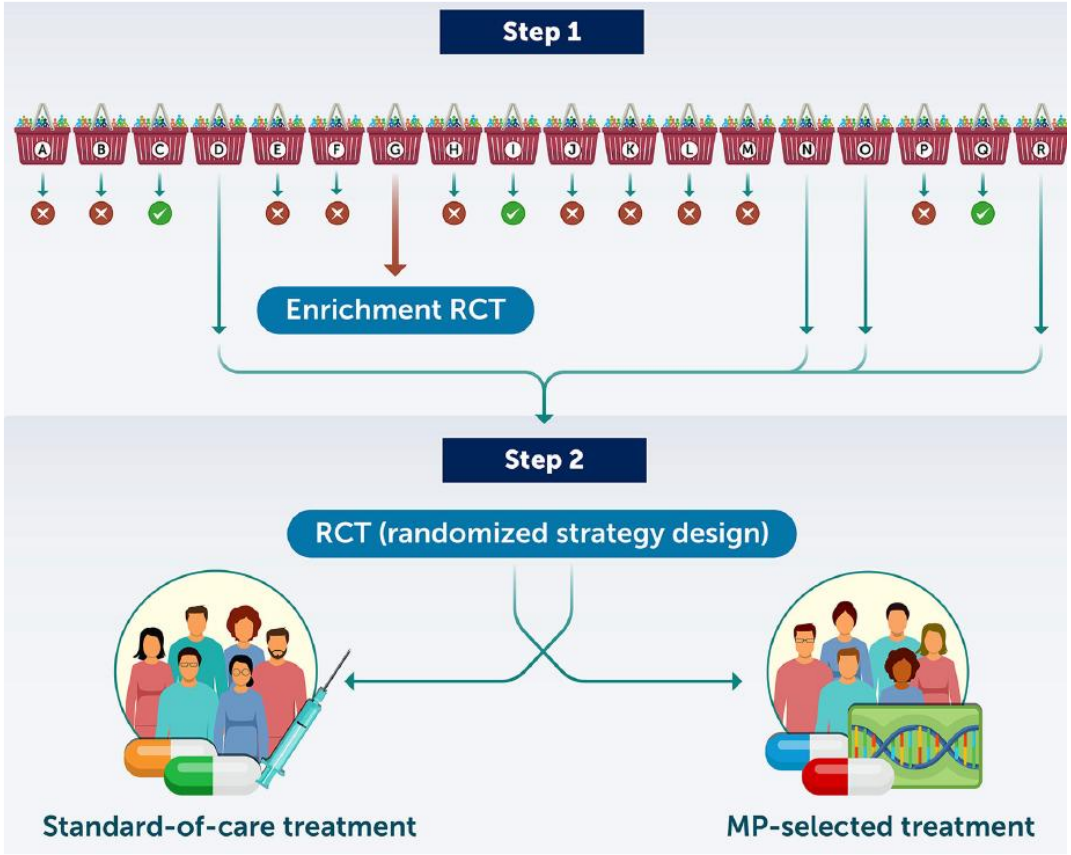
Ou F-S Journal of Thoracic Oncology. 2021; 16(4): 537-545





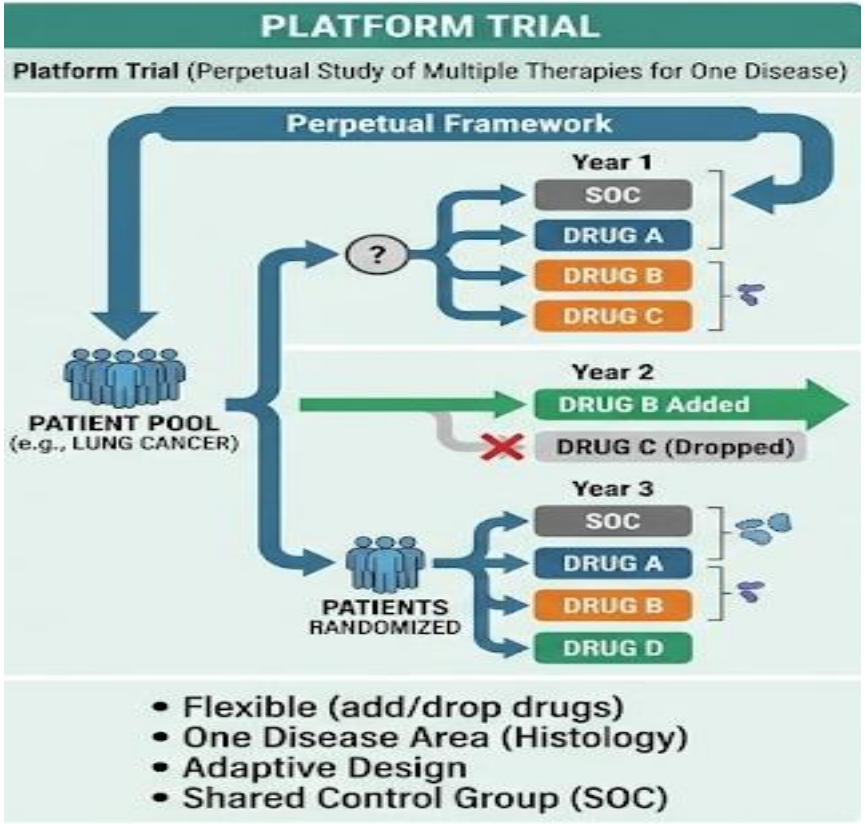
Ou F-S Journal of Thoracic Oncology. 2021; 16(4): 537-545

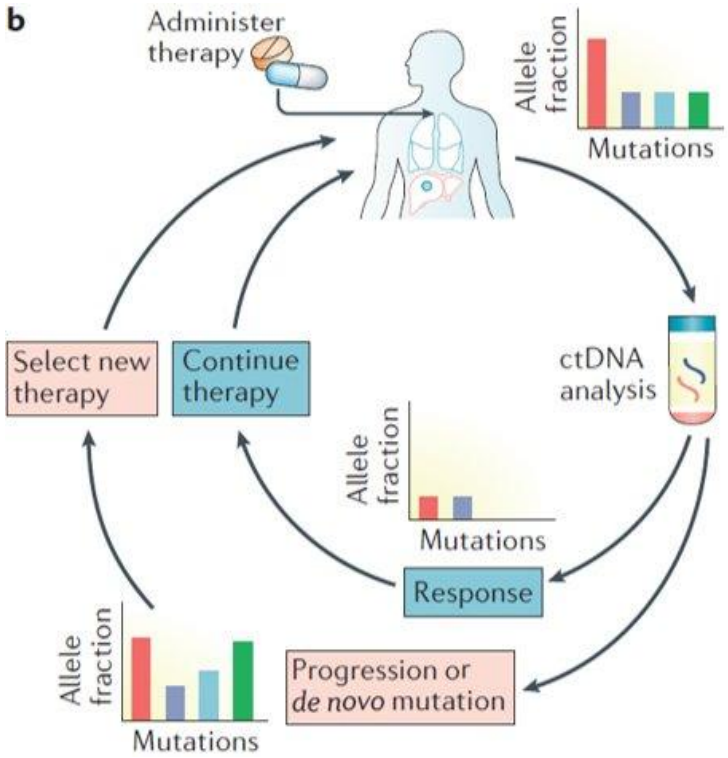
UTILIDAD CLÍNICA PREDICTIVA: ESTUDIOS PROSPECTIVOS



Freidlin B. Journal of Clinical Oncology. 2026, 44(7):515-7

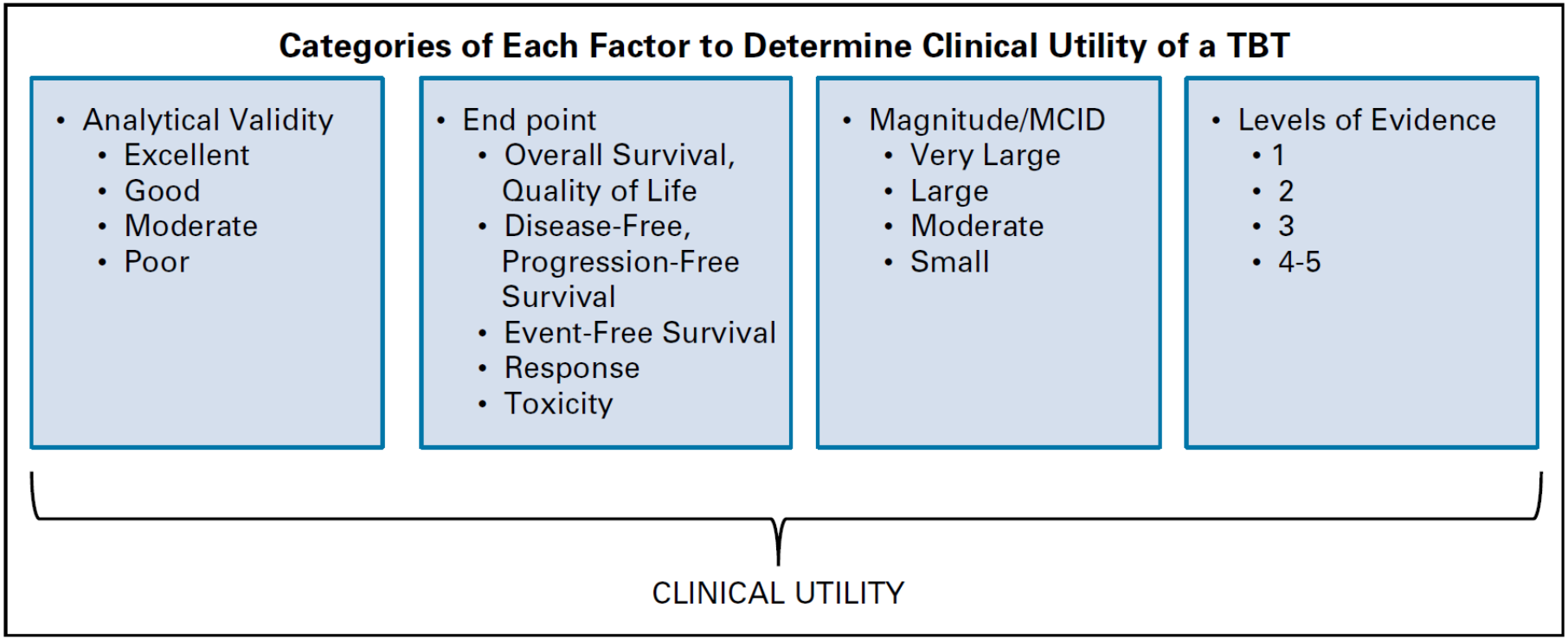
UTILIDAD CLÍNICA PREDICTIVA: ESTUDIOS PROSPECTIVOS





Wan JCM. Nature Reviews Cancer. 2017, 17(4): 223-238

VALIDACIÓN UTILIDAD CLÍNICA



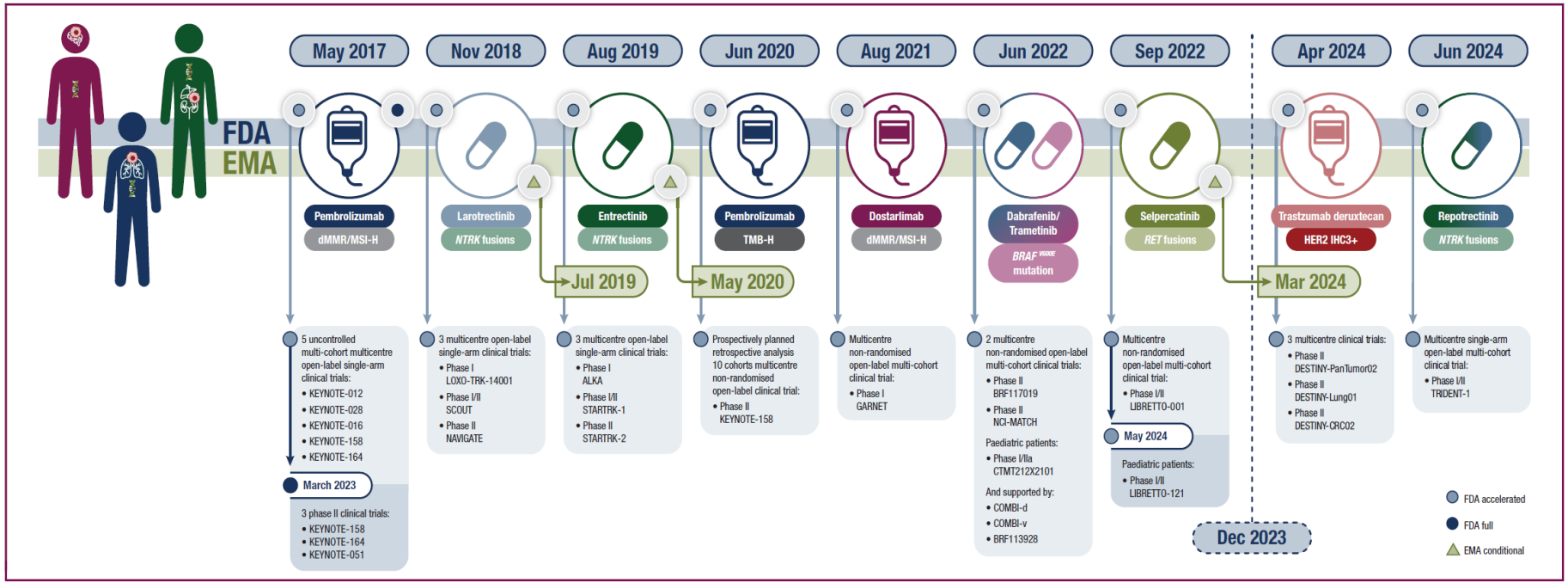
Hayes DF. J Clin Oncol. 2020; 39: 238-248

EVIDENCIA CIENTÍFICA UTILIDAD CLÍNICA BIOMARCADOR: ACCIONABILIDAD

Table 1. The ESCAT v2 Actionability Scale

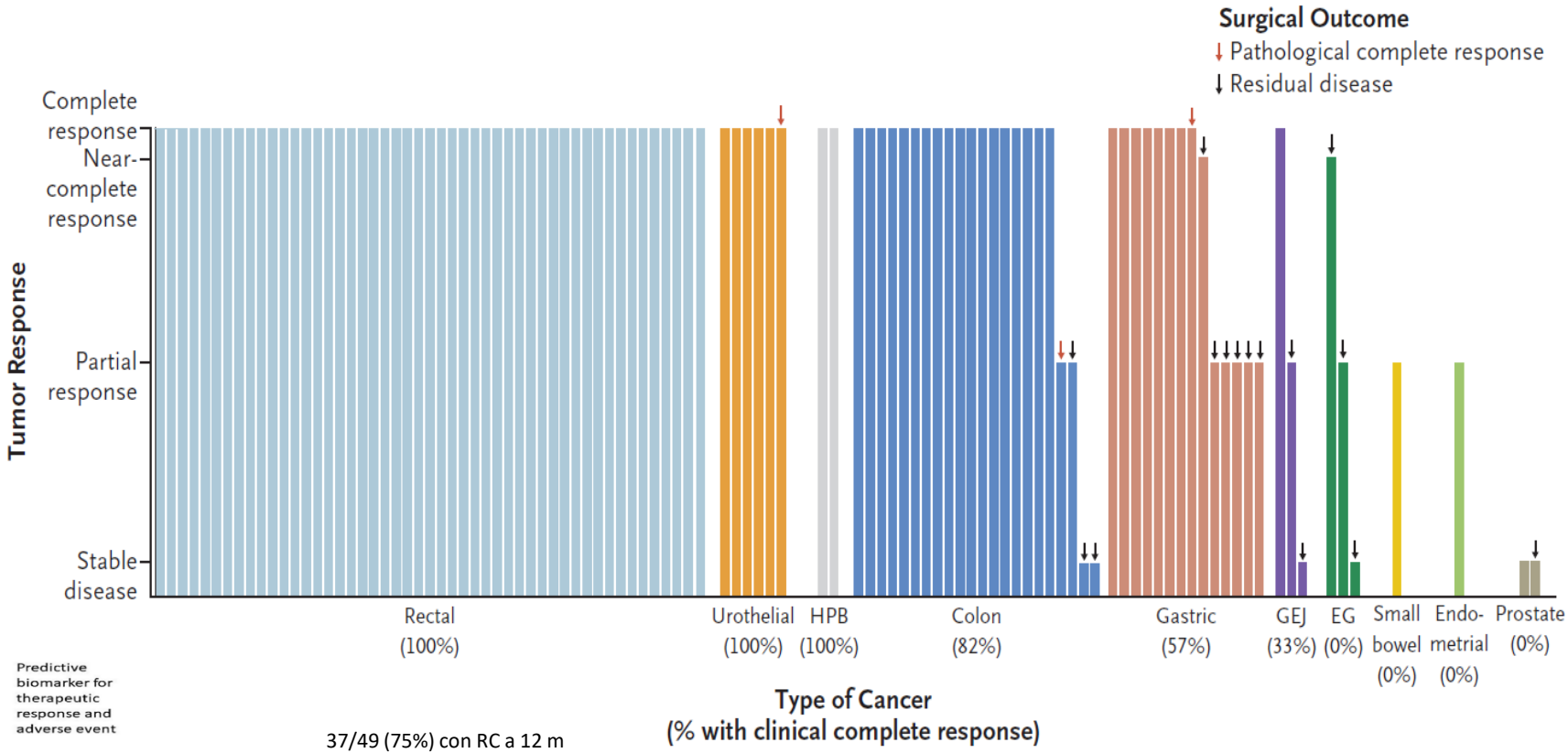
Tier	Clinical directive	Subtier	Category	Definition	Minimum evidence	Illustrative example
I	The matched therapy can be considered part of standard of care in eligible patients: testing for the biomarker is recommended and, when identified, should guide treatment selection. The clinical directive is identical across all three subtiers.	I-proven (I-P)	Tumour-specific randomised evidence	Biomarker—therapy match with demonstrated clinical benefit in a specified tumour type via prospective RCT with biomarker-based selection or stratification. Lowest level of uncertainty within tier I.	Prospective RCT; prespecified survival endpoint (OS, PFS, EFS, or DFS) met with statistical significance; clinically validated assay. Where the comparator is an established biomarker-guided standard of care, noninferiority or comparable efficacy is sufficient.	*ALK* rearrangement, *EGFR* exon 19 deletion or L858R, and *RET* fusion in advanced NSCLC
		I-inferred (I-I)	Tumour-specific nonrandomised evidence	Biomarker—therapy match evaluated within a single defined tumour type; benefit inferred from the magnitude of the treatment effect rather than measured against a concurrent comparator. Higher uncertainty than I-P.	Prospective nonrandomised trial(s) in the specified tumour type; prespecified time-to-event endpoint (PFS, OS, EFS, or DFS) clearly exceeding the best available benchmark for that tumour type and line; clinically validated assay. High ORR alone is supportive but not sufficient.	*BRAF* V600E as a predictive biomarker in treatment-naïve and pretreated *BRAF* V600E-mutant NSCLC
		I-extrapolated (I-E)	Multitumour evidence meeting ETAC-S	Biomarker—therapy match evaluated across multiple tumour types with consistent clinical activity meeting the ETAC-S criteria for tumour-agnostic use. Individual tumour type pairs may migrate to I-I or I-P as tumour-specific data mature.	Prospective multitumour trial(s); ETAC-S criteria met; clinically validated assay. Clinically meaningful ORR and DOR per tumour type are acceptable in place of tumour type-specific time-to-event outcomes.	*NTRK* fusions and larotrectinib across >20 tumour types (integrated ORR ~75%); MSI-H/dMMR and PD-(L)1 inhibitors across noncolorectal tumour types

Elali AE. Annals of Oncology. 2026. https://doi.org/10.1016/j.annonc.2026.09.008



Westphalen CB. Annals of Oncology. 2024; 35(11): 936-53

Fase II, dostarlimab neoadyuvante en cáncer I-III dMMR para evitar cirugía: 44% sdr. Lynch



Predictive biomarker for therapeutic response and adverse event

Treatment Decision

37/49 (75%) con RC a 12 m

Cerkek A. N Engl J Med, 2025. DOI: 10.1056/NEJMoa2404512

II	The biomarker–therapy match may be considered on a case-by-case basis, preferably with MTB endorsement, enrolment in a clinical trial or prospective registry should be explored where available.	II-A	Prospective interventional activity evidence	Protocol-assigned therapy in a prospective interventional study with predefined endpoints and tumour type-specific reporting; response-based (ORR ± DOR), without time-to-event survival benefit at the tier I standard.	Protocol-assigned therapy; predefined endpoints; systematic assessment; tumour type-specific cohort. *Post hoc* biomarker analyses of trials where therapy was not assigned on the basis of the biomarker do not qualify.	Anti-HER2 therapy in ERBB2-amplified salivary duct carcinoma
		II-B	High-quality real-world/ nonprospective activity evidence	Activity (and in some cases time-to-event benefit) observed in analyses not designed to test the specific biomarker–tumour combination as a primary hypothesis; benefit cannot be confidently attributed to the therapy without prospective demonstration.	≥2 independent datasets, nonoverlapping populations; validated assays; characterised treatment exposure; standardised endpoints; transparent handling of missing data. Comparability via biomarker ± comparison, credible external control, or consistent independent cohort.	Avapritinib in *PDGFRA*-altered high-grade glioma
		II-C	Replicated case-level activity evidence	Three or more evaluable patients across two or more independent sources with directionally consistent activity and functional support. Least certain category within tier II; MTB must state that uncertainty is elevated.	Three or more evaluable biomarker-positive patients; two or more independent sources; directionally consistent activity supported by preclinical functional data; clinical impact exceeding documented natural history.	—

Continued

Elali AE. Annals of Oncology. 2026. https://doi.org/10.1016/j.annonc.2026.09.008

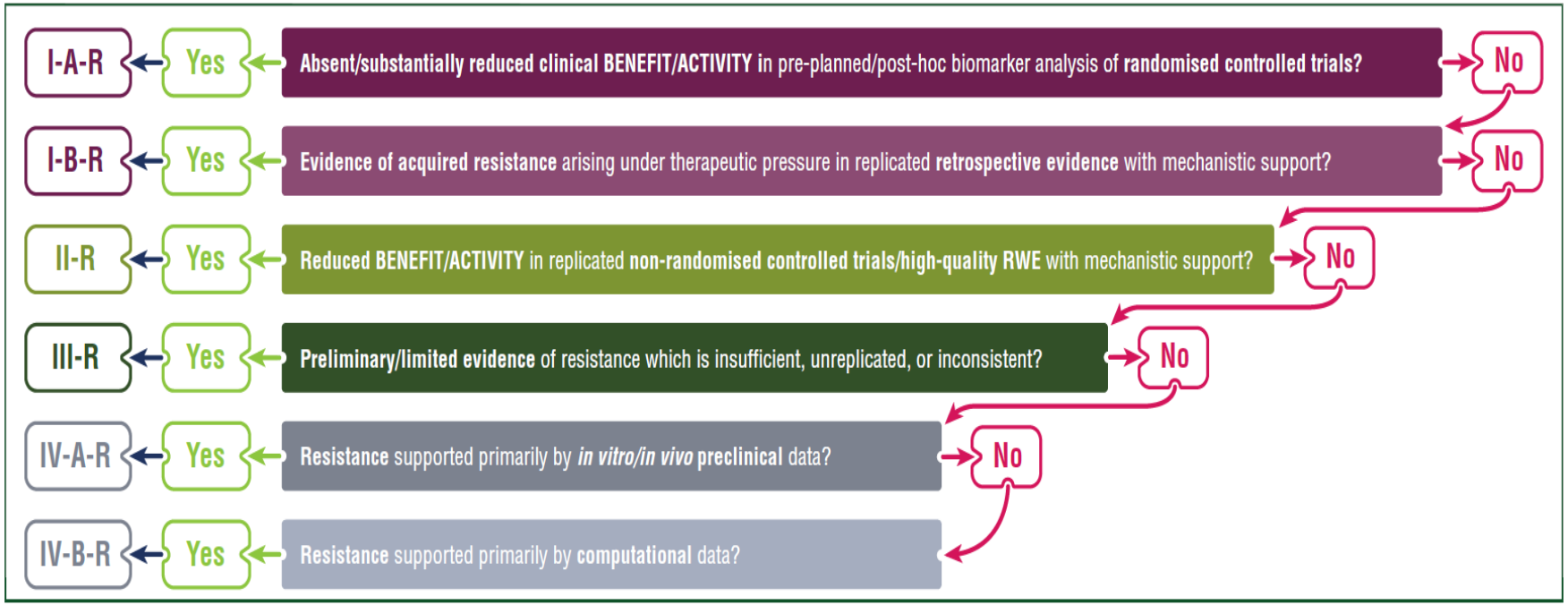


Elali AE. Annals of Oncology. 2026. https://doi.org/10.1016/j.annonc.2026.09.008

Table 2. The ESCAT v2 Resistance Scale

Tier	Clinical directive	Subtier	Level	Definition	Evidence requirements	Illustrative example
I-R	True contraindication: do not use this therapy, or substitute/sequence differently	I-A-R	Clinically validated	Absent or substantially diminished benefit in the biomarker-positive subgroup demonstrated by one or more adequately powered RCT or a biomarker analysis nested within an RCT.	One or more adequately powered RCT with preplanned or *post hoc* biomarker analysis. Endpoints: time-to-event (PFS, OS, EFS, and DFS) preferred; response-based (ORR, DOR, pCR, and RCB) acceptable when time-to-event data are unavailable, immature, or confounded.	Activating *RAS* mutations, predicting resistance to anti-EGFR monoclonal antibodies
		I-B-R	Clinically validated	Negligible residual benefit in acquired resistance, demonstrated by replicated findings across two or more independent retrospective clinical datasets from different institutions with nonoverlapping patients, a well-characterised molecular mechanism, and on-progression biomarker sampling.	Two or more independent, methodologically rigorous retrospective datasets with documented temporal relationship between biomarker detection and resistance, and a well-characterised mechanism. Endpoints: time-to-event preferred; response-based acceptable.	*MET* amplification as resistance alteration secondary to osimertinib

Elali AE. Annals of Oncology. 2026. https://doi.org/10.1016/j.annonc.2026.09.008

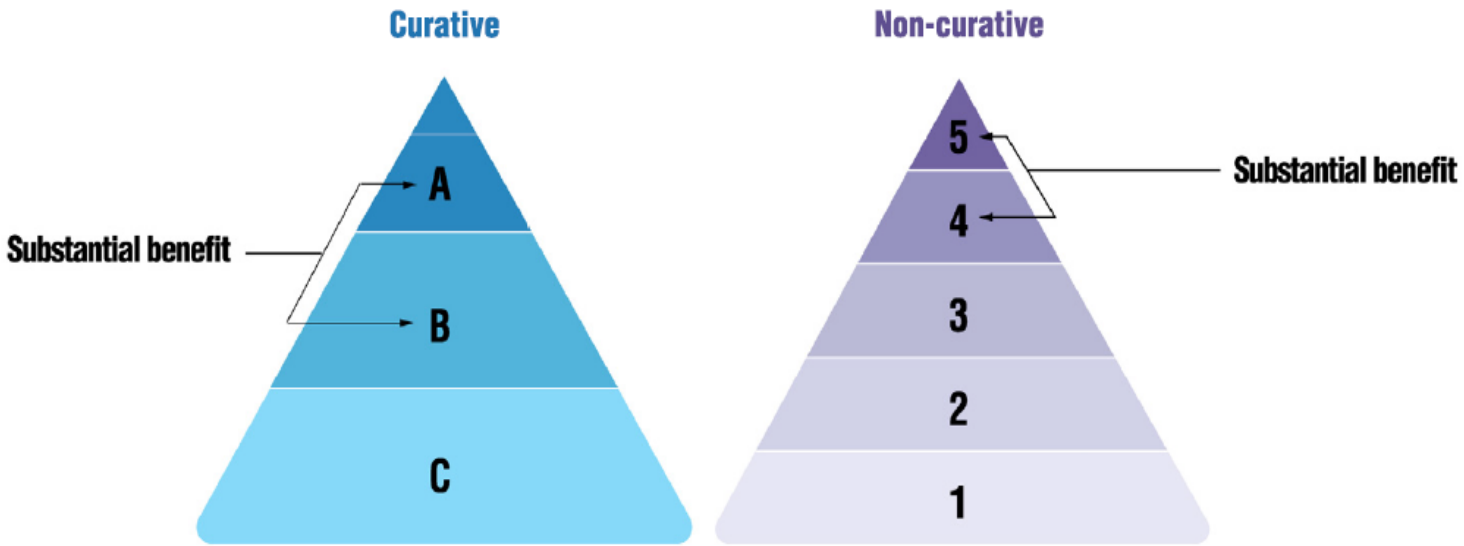


Elali AE. Annals of Oncology. 2026. https://doi.org/10.1016/j.annonc.2026.09.008

ESMO-MCBS v2.0

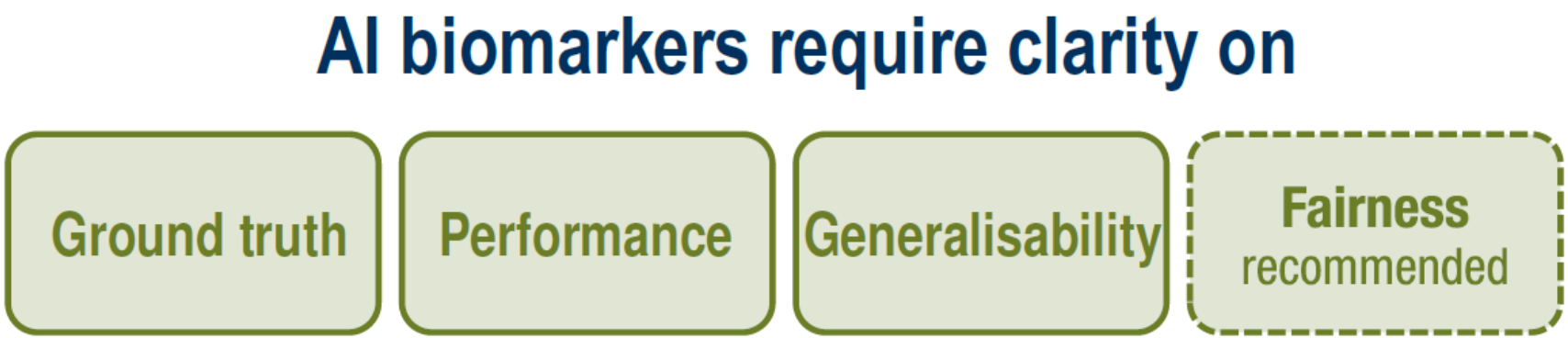
ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale



Cherny NI. Annals of Oncology. 2025, 36(8):866-908

VALIDACIÓN AI-BASED BIOMARKER

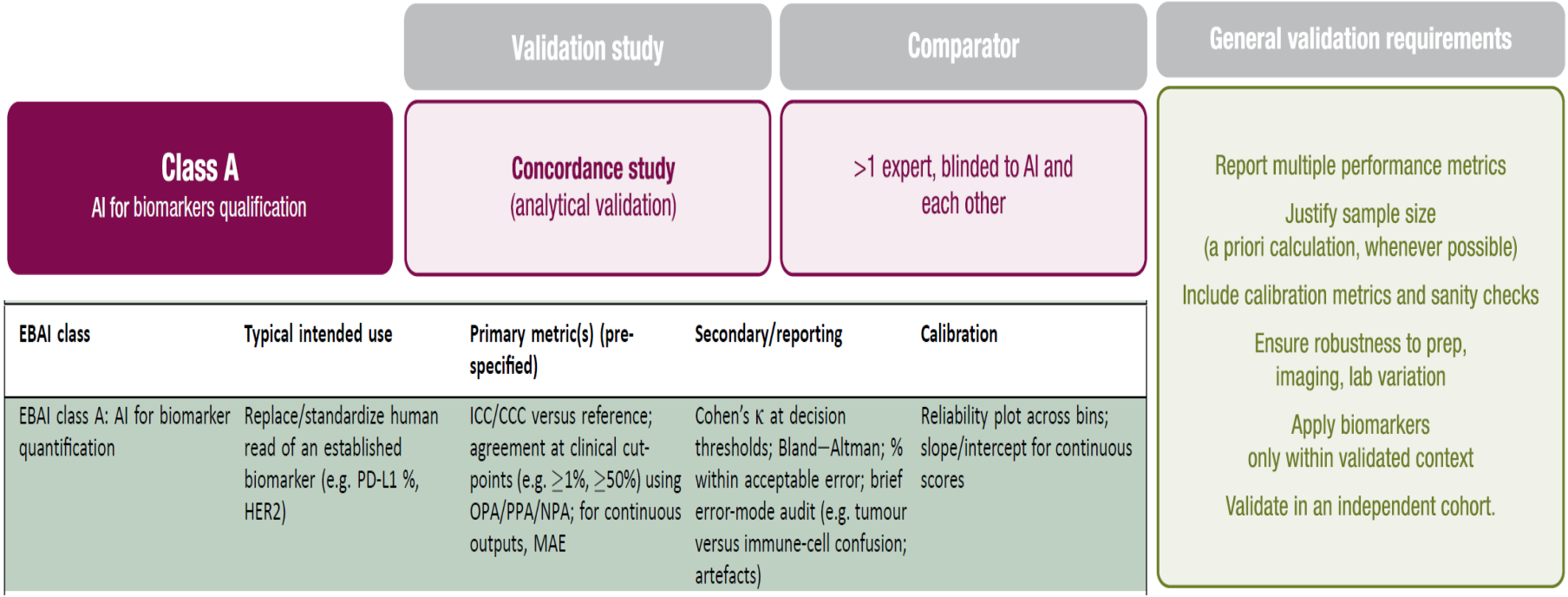


COMPARADOR **DESEMPEÑO** **VALIDACIÓN EXTERNA** **SESGOS COHORTE**

VALIDACIÓN COMPLETA

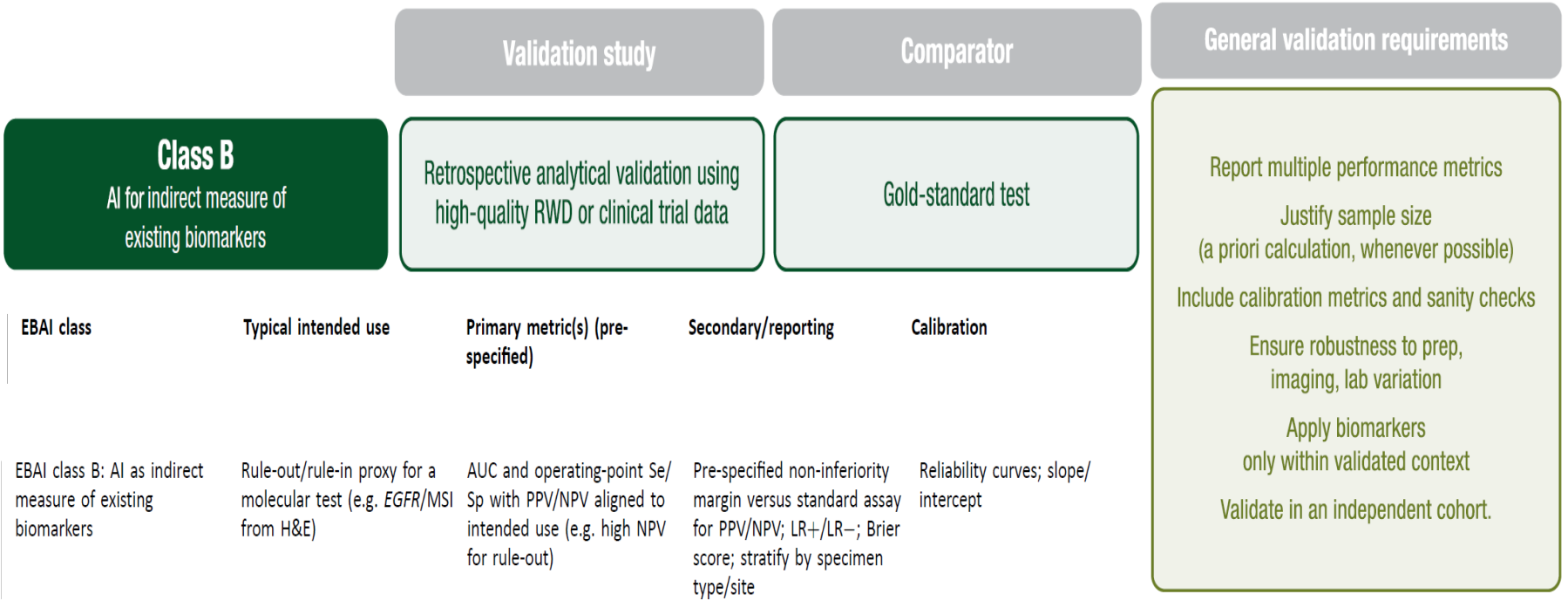
EXPLAINABILITY: BLACK-BOX, CÓMO FUNCIONAN LOS ALGORITMOS
COSTE-EFECTIVIDAD

Aldea M. Annals of Oncology. 2026; 37(3): 414-25



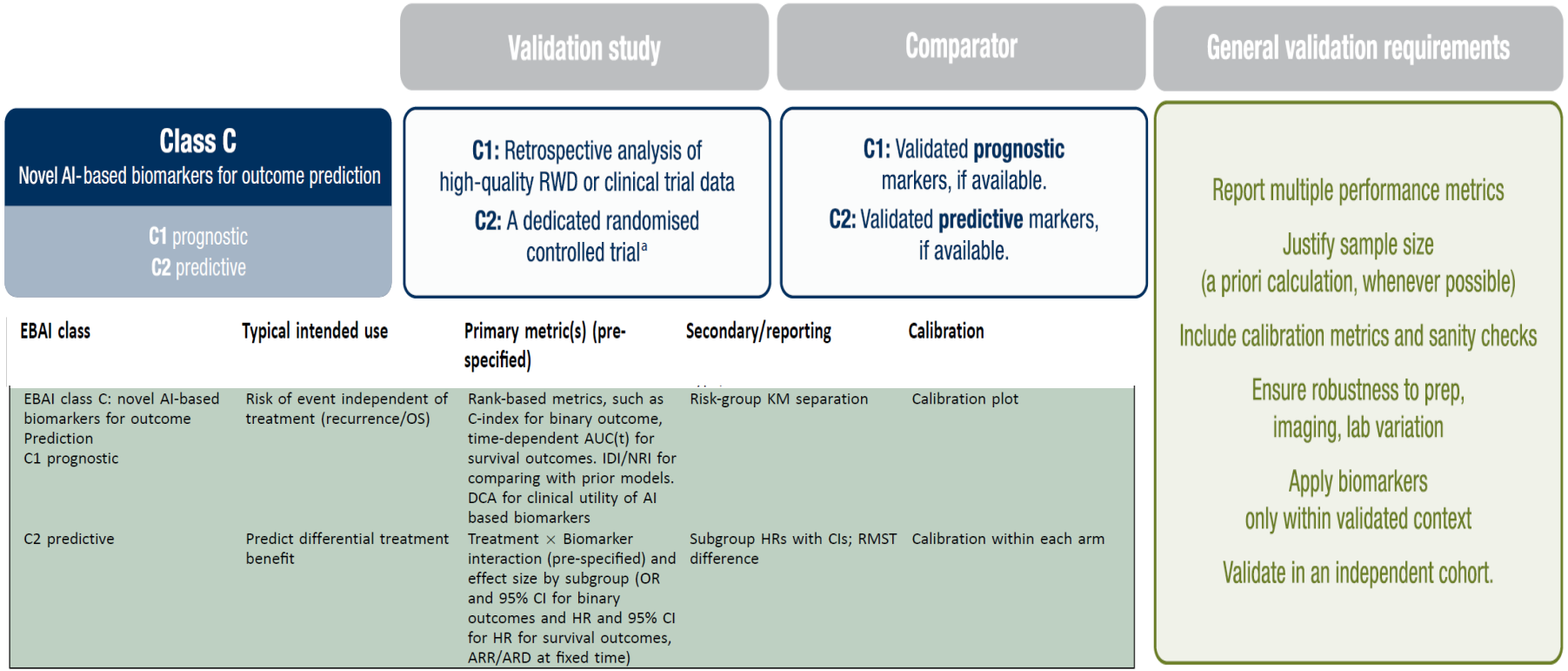
EBAI class	Typical intended use	Primary metric(s) (pre-specified)	Secondary/reporting	Calibration
EBAI class A: AI for biomarker quantification	Replace/standardize human read of an established biomarker (e.g. PD-L1 %, HER2)	ICC/CCC versus reference; agreement at clinical cut-points (e.g. ≥1%, ≥50%) using OPA/PPA/NPA; for continuous outputs, MAE	Cohen's κ at decision thresholds; Bland–Altman; % within acceptable error; brief error-mode audit (e.g. tumour versus immune-cell confusion; artefacts)	Reliability plot across bins; slope/intercept for continuous scores

Aldea M. Annals of Oncology. 2026; 37(3): 414-25



EBAI class	Typical intended use	Primary metric(s) (pre-specified)	Secondary/reporting	Calibration
EBAI class B: AI as indirect measure of existing biomarkers	Rule-out/rule-in proxy for a molecular test (e.g. *EGFR*/MSI from H&E)	AUC and operating-point Se/Sp with PPV/NPV aligned to intended use (e.g. high NPV for rule-out)	Pre-specified non-inferiority margin versus standard assay for PPV/NPV; LR+/LR−; Brier score; stratify by specimen type/site	Reliability curves; slope/intercept

Aldea M. Annals of Oncology. 2026; 37(3): 414-25



EBAI class	Typical intended use	Primary metric(s) (pre-specified)	Secondary/reporting	Calibration
EBAI class C: novel AI-based biomarkers for outcome Prediction C1 prognostic	Risk of event independent of treatment (recurrence/OS)	Rank-based metrics, such as C-index for binary outcome, time-dependent AUC(t) for survival outcomes. IDI/NRI for comparing with prior models. DCA for clinical utility of AI based biomarkers	Risk-group KM separation	Calibration plot
C2 predictive	Predict differential treatment benefit	Treatment × Biomarker interaction (pre-specified) and effect size by subgroup (OR and 95% CI for binary outcomes and HR and 95% CI for HR for survival outcomes, ARR/ARD at fixed time)	Subgroup HRs with CIs; RMST difference	Calibration within each arm

Aldea M. Annals of Oncology. 2026; 37(3): 414-25

IMPLEMENTACIÓN BIOMARCADOR PREDICTIVO

Salah-Eddin-Al-Batran. ESMO 2026.

journey

CLDN18.2: From discovery to first approval: 23 years

2001

Molecular and Cellular Biology
Tomoaki Niimi et al.
Identification of CLDN18.2 as a stomach-specific isoform

2008

Clinical Cancer Research
Uğur Şahin, Özlem Türeci et al.
Identification of CLDN18.2 as pan-tumor therapeutic target

2016

ASCO Annual Meeting
Salah-Eddin Al-Batran
FAST: First clinical proof of concept for targeting CLDN18.2 (IMAB362)

2023

ASCO GI
Kohei Shitara
SPOTLIGHT: First positive phase III trial on this CLDN18.2 antibody (zolbetuximab)

2024

First regulatory approval of a CLDN18.2-targeted therapy: zolbetuximab in Japan

2026

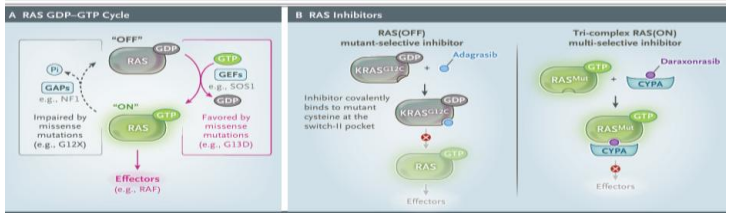
ESMO Congress
Rui-Hua Xu and Kohei Shitara
CLARITY-Gastric 01 and G-HOPE-001: First Phase III results with the CLDN18.2-targeted ADCs (sonesitatug vedotin and Arcotatug tavatecan)

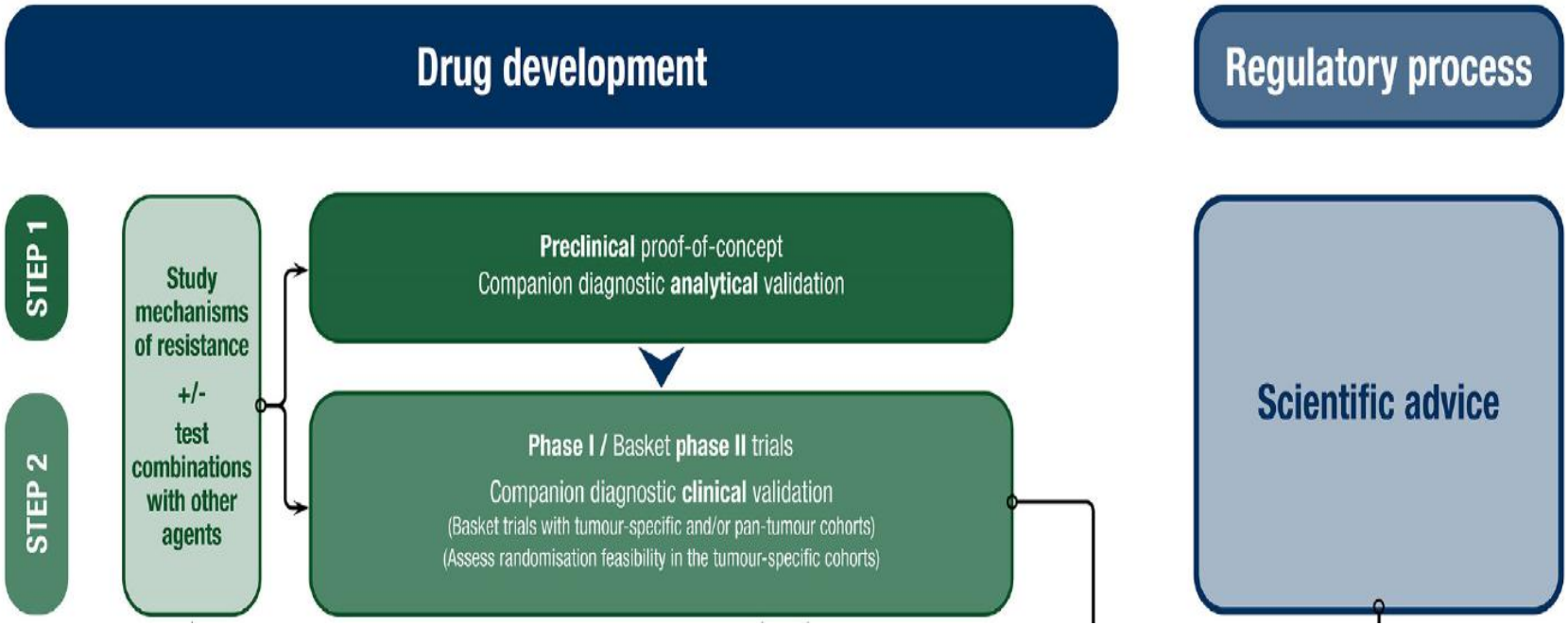
Malignant Activation of a K-ras Oncogene in Lung Carcinoma But Not in Normal Tissue of the Same Patient

Barbacid M. 1982

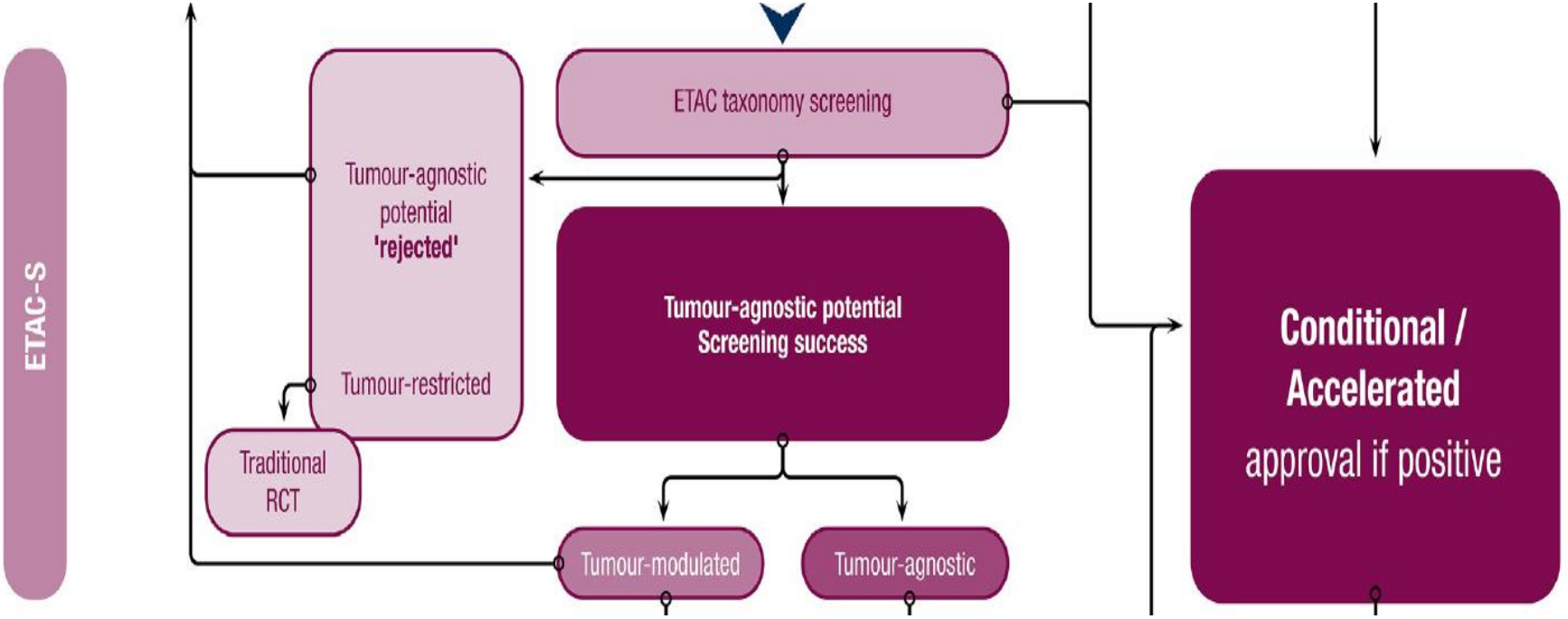


Kras-i/d 2021

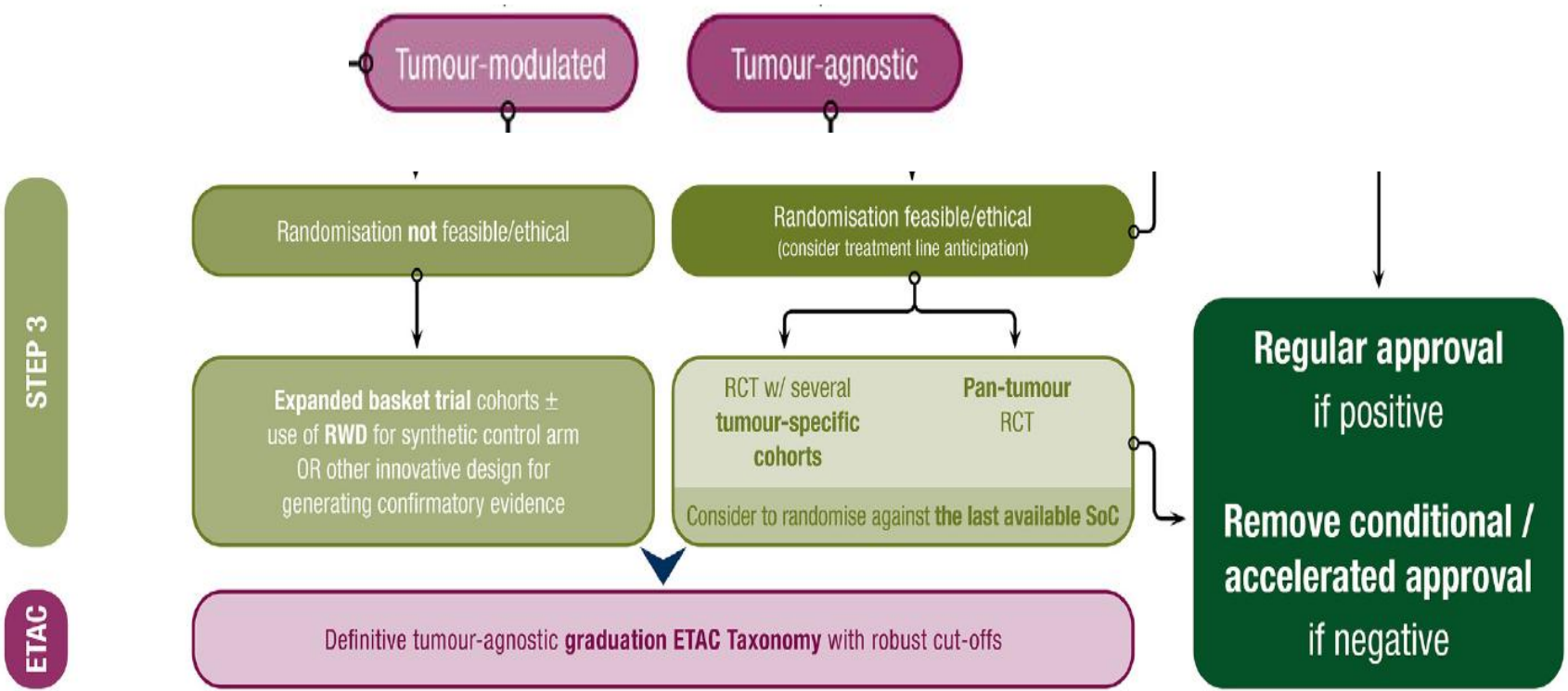




Westphalen CB. Annals of Oncology. 2024; 35(11): 936-53



Westphalen CB. Annals of Oncology. 2024; 35(11): 936-53



Westphalen CB. Annals of Oncology. 2024; 35(11): 936-53

CONCLUSIÓN

Utilidad clínica de Biomarcador/TBT/AI-based Biomarker cambia la práctica asistencial

Requiere metodología específica

Acortar tiempo manteniendo rigor científico

GRACIAS