Caratterizzazione genomica delle lesioni

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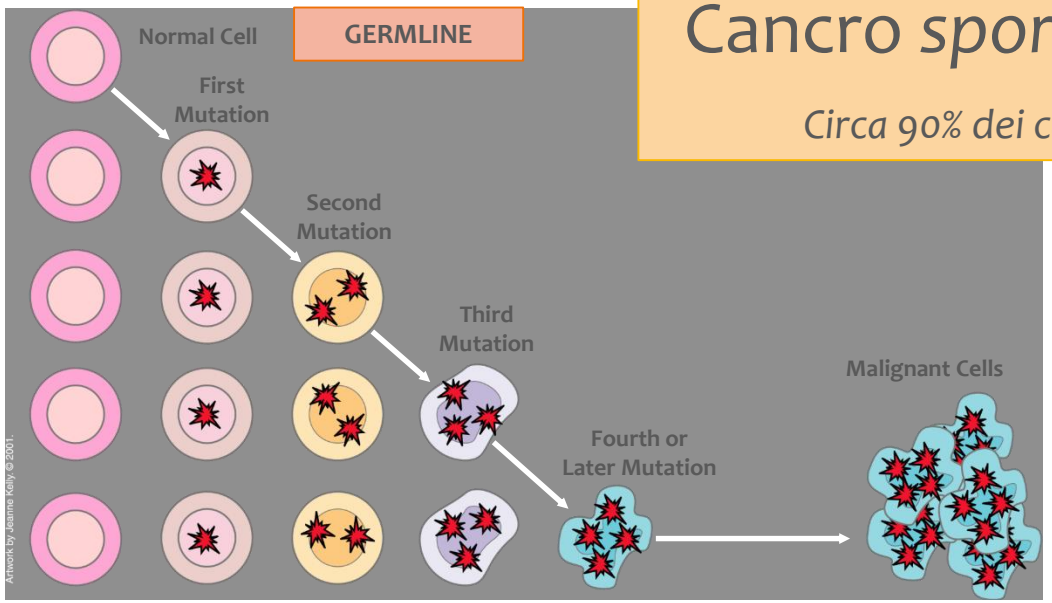
Università di Bologna – DIMEC

Il cancro è una malattia genetica

Cancro *sporadico*

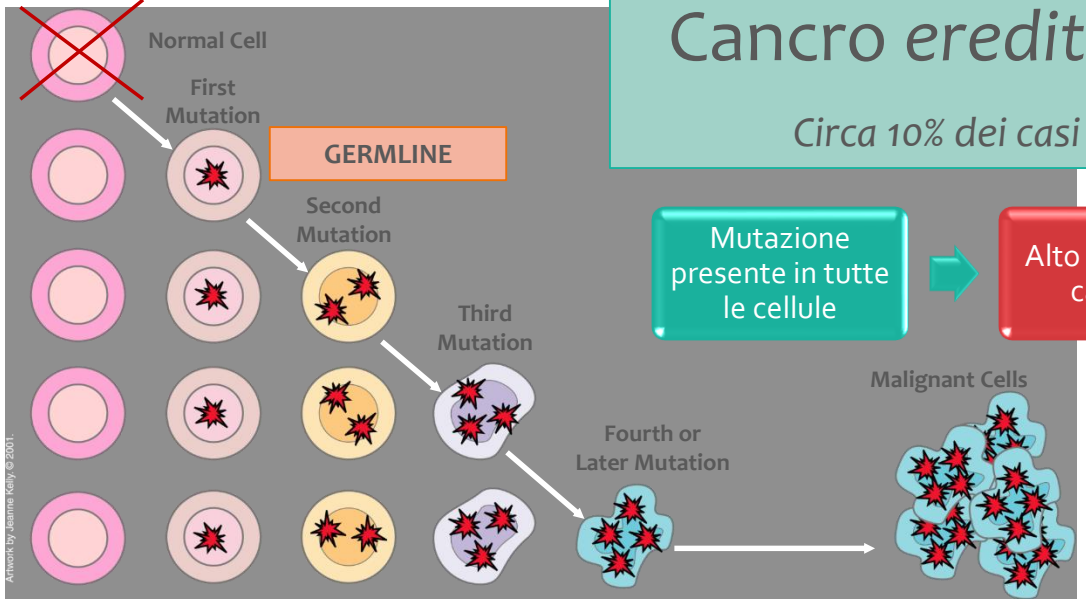
Circa 90% dei casi



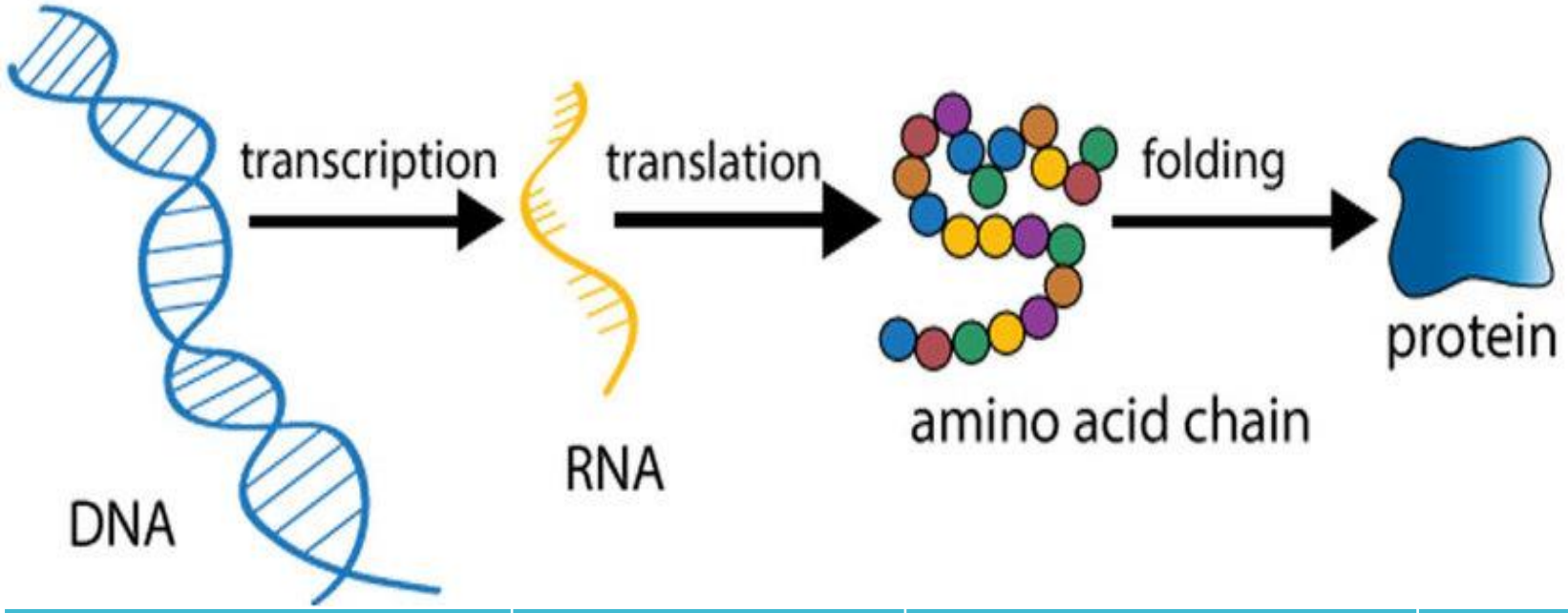
Cancro *ereditario*

Circa 10% dei casi

Mutazione presente in tutte le cellule → Alto rischio di cancro

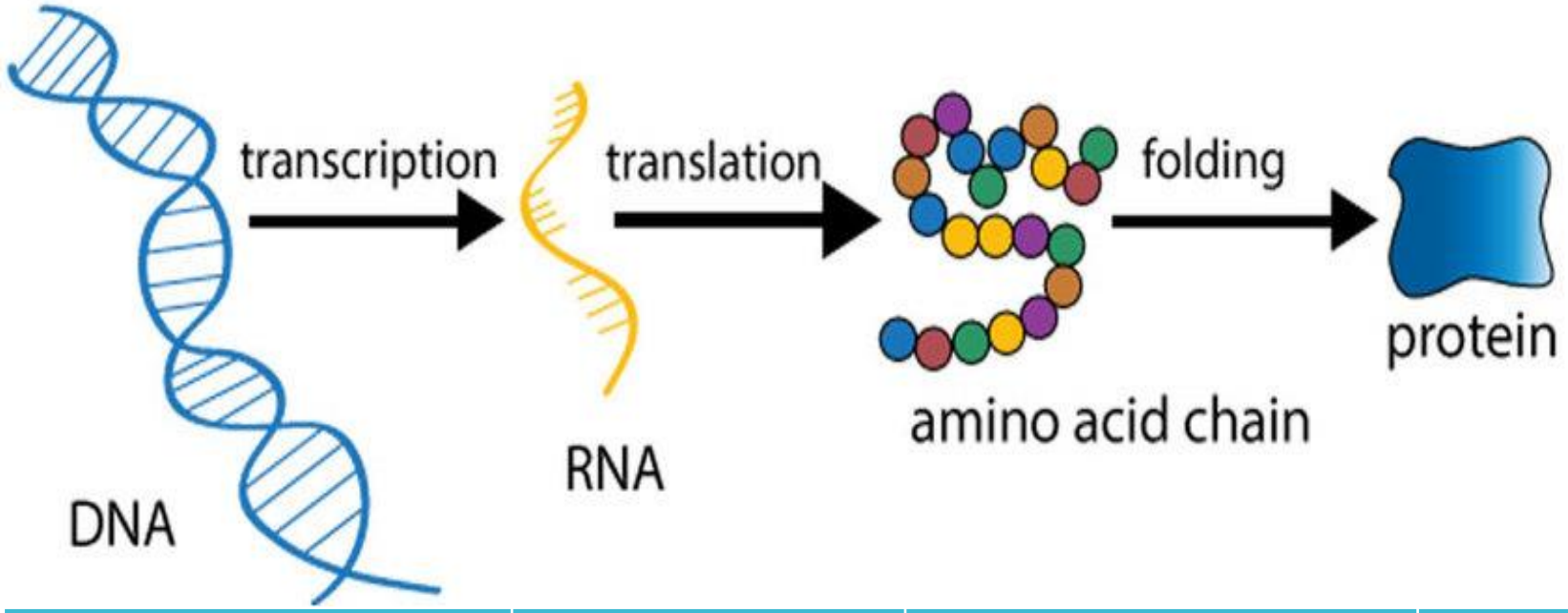


Test genomici nel carcinoma mammario



DNA	RNA	Proteine	Uso	Significato	Stadio
ISH HER2		IHC: ER, PgR, HER2,...	Consolidato	Prognostico/ predittivo	Tutti
	Test multigenici prognostici		In via di introduzione	Prognostico ai fini della terapia	Precoce
Analisi NGS di centinaia di geni/intero genoma			Sperimentale	Terapia a bersaglio molecolare	Avanzato

Test genomici nel carcinoma mammario



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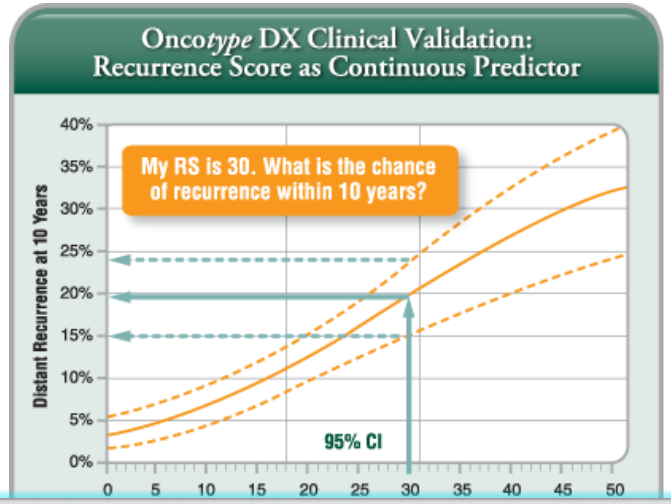
Assay	Classifiers (*n* genes)	Platform	Binary (high vs. low)	Decentralized testing	Recommended by ASCO clinical practice guideline[25] (node-negative)	Validated in N0 and N1	Utility in late recurrence
Oncotype DX[a]	16	qPCR	No	No	Evidence quality: high Strength recommendation: strong	Yes	Possibly
Prosigna[b]	50	nCounter	No	Yes	Evidence quality: high Strength recommendation: strong	Yes	Yes
Mammaprint[c]	70	Microarray or qPCR	Yes	No	Evidence quality: intermediate Strength recommendation: moderate	Yes	No
EndoPredict[d]	8	qPCR	Yes	Yes	Evidence quality: intermediate Strength recommendation: moderate	Yes	Possibly
Breast Cancer Index[e]	7	qPCR	Yes	No	Evidence quality: intermediate Strength recommendation: moderate	No	Yes
Genomic Grade Index[f]	97	Microarray	Yes	No	Not discussed	No	No

[a] Genomic Health, Redwood City, CA, U.S.A.
[b] NanoString Technologies, Seattle, WA, U.S.A.
[c] Agendia, Irvine, CA, U.S.A.
[d] Myriad Genetics, Salt Lake City, U.S.A.
[e] bioTheranostics, San Diego, CA, U.S.A.
[f] MapQuant Dx: Ipsogen, Marseille, France.
qPCR = quantitative polymerase chain reaction.



Assay	Pivotal study or studies	Study design	Sample size (*n*)	Intervention	Clinical utility
Oncotype DX[a]	NSABP B20[4]	Prospective-retrospective	651	Tamoxifen ± CMF	▪ Significant benefit to chemotherapy when recurrence score is high; limited benefit when recurrence score is low ▪ Very favourable prognosis with endocrine therapy alone when recurrence score is 10 or less
	TAILORx[5]	Prospective	1626	Endocrine for 5 years	
Prosigna[b] (PAM50 ROR)	ABCSG-8 and TransATAC[6]	Prospective-retrospective	2137	Endocrine for 5 years	▪ Very favourable prognosis with endocrine therapy alone when risk-of-recurrence score is low or subtype is luminal A
	DBCG[7]	Retrospective	2749	Endocrine for 5 years	
MammaPrint[c]	MINDACT[8]	Prospective randomized controlled trial	6693 (entire study) 2142 (randomized component)		▪ Discordance in clinical and genomic results randomized to chemotherapy or not ▪ Favourable prognosis with or without adjuvant chemotherapy when 70-gene signature is low-risk
EndoPredict[d]	ABCSG-6 and ABCSG-8[9]	Prospective-retrospective	1702	Endocrine for 5 years	▪ Very favourable prognosis with endocrine therapy alone when EPclin score is low
Breast Cancer Index[e]	CCTG MA.17[10]	Nested case–control study	249	Letrozole vs. placebo after 5 years of tamoxifen	▪ Greater benefit to extended hormonal therapy when the Breast Cancer Index is high

CMF = cyclophosphamide, methotrexate, 5-fluorouracil; ROR = risk of recurrence; ABCSG = Austrian Breast and Colorectal Cancer Study Group; DBCG = Danish Breast Cancer Group; CCTG = Canadian Cancer Trials Group.
[a] Genomic Health, Redwood City, CA, U.S.A.
[b] NanoString Technologies, Seattle, WA, U.S.A.
[c] Agendia, Irvine, CA, U.S.A.
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CHIA, S.K.L.. Clinical application and utility of genomic assays in early-stage breast cancer: key lessons learned to date. Current Oncology, [S.l.], v. 25, p. S125-S130, june 2018

BreastCare

Review Article

Breast Care 2017;12:102–107
DOI: 10.1159/000475698

Published online: April 26, 2017

St. Gallen/Vienna 2017: A Brief Summary of the Consensus Discussion about Escalation and De-Escalation of Primary Breast Cancer Treatment

Michael Gnant[a] Nadia Harbeck[b] Christoph Thomssen[c]

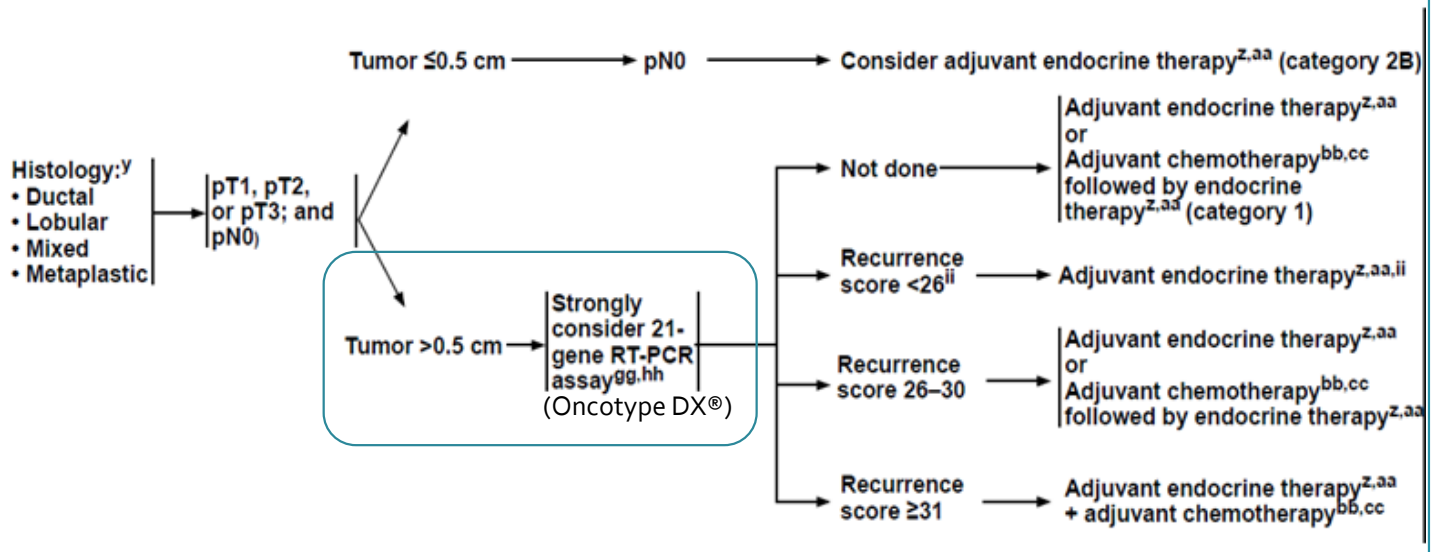
[a]Department of Surgery and Comprehensive Cancer Center Vienna, Medical University of Vienna, Vienna, Austria;
[b]Breast Center, Department of Obstetrics and Gynecology, University of Munich (LMU), Munich, Germany;
[c]Department of Gynecology, Martin-Luther-University, Halle/Saale, Germany

Test	Omission of chemotherapy in N0 yes / no / abstain	Omission of chemotherapy in N+ (1–3 LN) yes / no / abstain
EndoPredict® (EPclin®) low risk	*not voted*	20% / 66% / 14%
MammaPrint® low risk	*not voted*	55.1% / 34.7% / 10.2%
Onkotype DX® low risk	87.8% / 10.2% / 2%	55.6% / 33.3% / 11.1%
Onkotype DX® intermediate risk	22.4% / 67.3% / 10.2%	6.3% / 87.5% / 6.3%
Prosigna® low risk	*not voted*	30.8% / 50% / 19.2%

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2018
Invasive Breast Cancer

SYSTEMIC ADJUVANT TREATMENT: NODE-NEGATIVE - HORMONE RECEPTOR-POSITIVE - HER2-NEGATIVE DISEASE[c]



NICE National Institute for Health and Care Excellence

Diagnostics guidance [DG34] Published date: December 2018

Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer

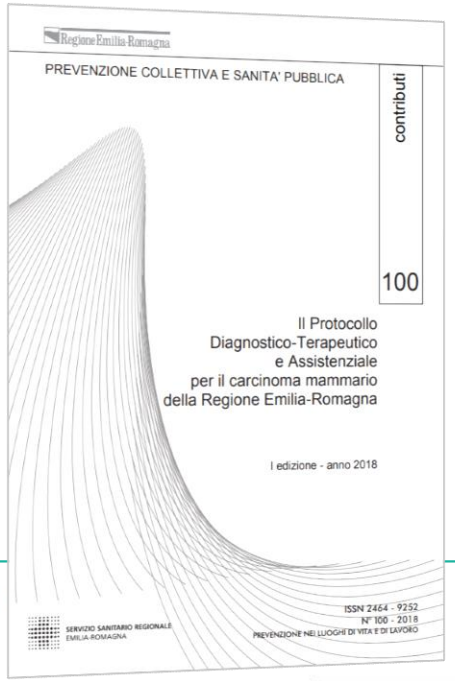
1.1 EndoPredict (EPclin score), Oncotype DX Breast Recurrence Score and Prosigna are recommended as options for guiding adjuvant chemotherapy decisions for people with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative and lymph node (LN)-negative (including micrometastatic disease; see section 5.4) early breast cancer, only if:

- they have an intermediate risk of distant recurrence using a validated tool such as PREDICT or the Nottingham Prognostic Index
- information provided by the test would help them choose, with their clinician, whether or not to have adjuvant chemotherapy taking into account their preference
- the companies provide the tests to the NHS with the discounts agreed in the access proposals and
- clinicians and companies make timely, complete and linkable record-level test data available to the National Cancer Registration and Analysis Service as described in the data collection arrangements agreed with NICE (see section 5.29).

1.2 MammaPrint is not recommended for guiding adjuvant chemotherapy decisions for people with ER-positive, HER2-negative and LN-negative early breast cancer because it is not cost effective.

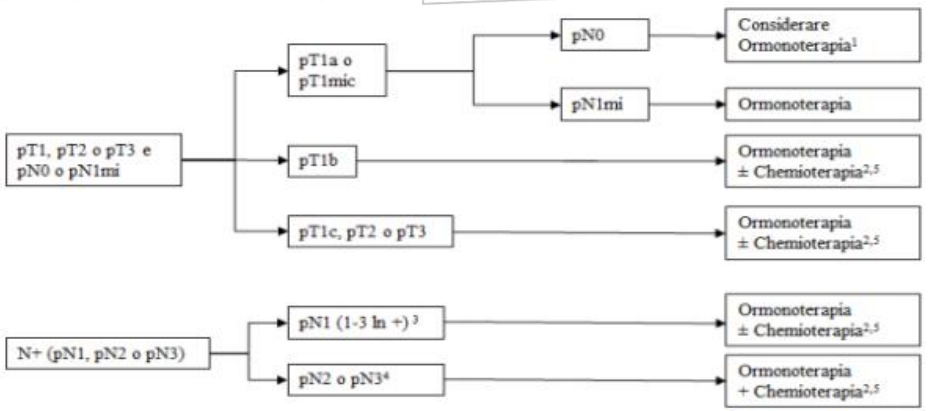
1.3 IHC4+C is not recommended for guiding adjuvant chemotherapy decisions for people with ER-positive, HER2-negative and LN-negative early breast cancer because the analytical validity of the test is uncertain.

Il Consiglio Superiore di Sanità del Ministero della Salute ha prodotto nel 2017 un documento "La Prescrizione dei Test Molecolari Multigenici Prognostici di Tumori (TMMP) della Mammella", che specifica che in Italia i TMMP non sono al momento inseriti tra i Livelli Essenziali di Assistenza (LEA) e quindi non sono rimborsabili; sono utilizzati senza specifiche regole istituzionali, ma sulla base delle esigenze cliniche su singoli casi e della possibilità delle pazienti di provvedere direttamente a coprirne il costo. Per l'introduzione nella pratica clinica come prestazione offerta dal SSN occorre tuttavia una regolamentazione che ne governi l'esecuzione, la qualità e l'applicazione a tutela delle pazienti, nonché un'analisi dei costi nell'ottica di una politica economico sanitaria efficace ed efficiente. In tale documento sono pertanto prodotte alcune raccomandazioni riportate nell'Allegato n. 4.



Trattamento sistemico adiuvante

Malattia ER+ e/o PR +, HER2-



Note:

1. Si può considerare di non prescrivere terapia se età>75 aa e/o se G1, Ki-67<15%, elevati livelli di ER e PR (> 50%), presenza di comorbidità;
2. L'aggiunta della chemioterapia all'ormonoterapia adiuvante può essere considerata soprattutto se presente uno o più fattori seguenti: G3, Ki-67 alto (superiore al 20%), bassi livelli di ER (<10%) e PR (<20%);
3. La valutazione della categoria di rischio in base ai predittori genomici (Oncotype, Mammaprint ecc.) potrebbe essere utilizzata in caso di dubbio, ma non è al momento rimborsata dal SSN;

Work in progress (HTA - EUnetHTA)

- Laser al triborato di litio (LBO) per la vaporizzazione fotoselettiva della prostata nel trattamento dell'iperplasia prostatica benigna - **Lithium triborate (LBO) laser for PVP in the treatment of Benign Prostatic Hyperplasia (BPH)**
- Defibrillatore indossabile (WCD) per la prevenzione primaria e secondaria nei pazienti a rischio di morte improvvisa - **Wearable cardioverter defibrillator (WCD) therapy in primary and secondary prevention of sudden cardiac arrest in patients at risk**
- Test prognostici multigenici per guidare la decisione sulla chemioterapia adiuvante nel tumore al seno in stadio precoce - **Multigenic prognostic tests to guide the decision on adjuvant chemotherapy in early stage breast cancer**

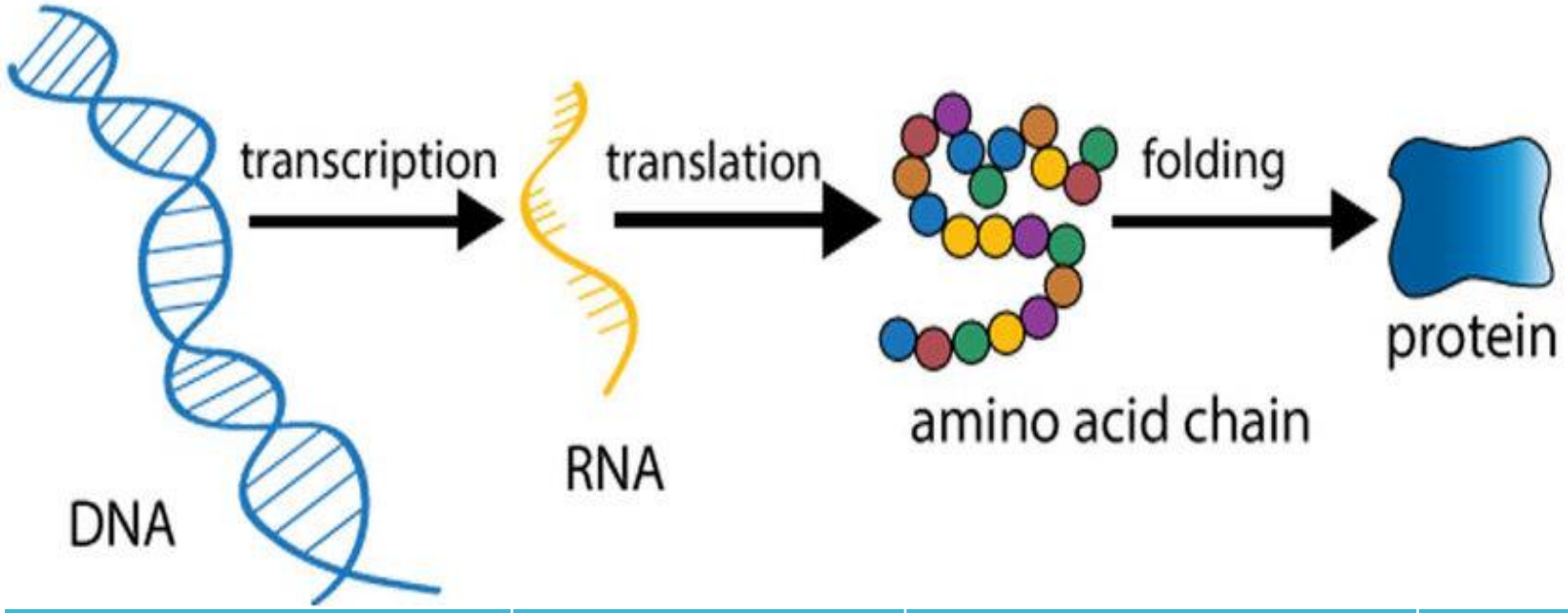
Nuove tecnologie / **New Technologies:**

- Chirurgia metabolica per il trattamento del diabete mellito di tipo 2 (DM2) indipendentemente dall'indice di massa corporea - **Bariatric surgery for patients with type 2 diabetes regardless of body mass index**
- Sistema CGM Eversense XL: sistema di monitoraggio glicemico continuo in tempo reale (rtCGM) in pazienti con diabete mellito trattati con insulina - **Eversense XL system CGM: Continuous glucose monitoring (CGM real-time) in patients with diabetes mellitus treated with insulin**
- Elecsys® Preeclampsia (sFlt-1 & PlGF): Test per la diagnosi della preeclampsia - **Elecsys®sFlt-1/PlGF (Preeclampsia): test in preeclampsia diagnosis**
- SIRIO H3: sistema di navigazione virtuale a supporto di procedure radiologiche con accesso percutaneo - **SIRIO H3: virtual navigation system to support radiological procedures with percutaneous access**
- Elekta Unity: acceleratore lineare con risonanza magnetica per terapia adattativa - **Elekta Unity: Adaptive radiotherapy with the combination of MR imaging and linac**

HTA

- Attività HTA
- HS Horizon Scanning
- RIHTA Rete Italiana HTA
- Ambiente di collaborazione
- Dispositivi medici
- Attività di Ricerca
- Articoli e pubblicazioni
- Work in progress (HTA - EUnetHTA)

Test genomici nel carcinoma mammario



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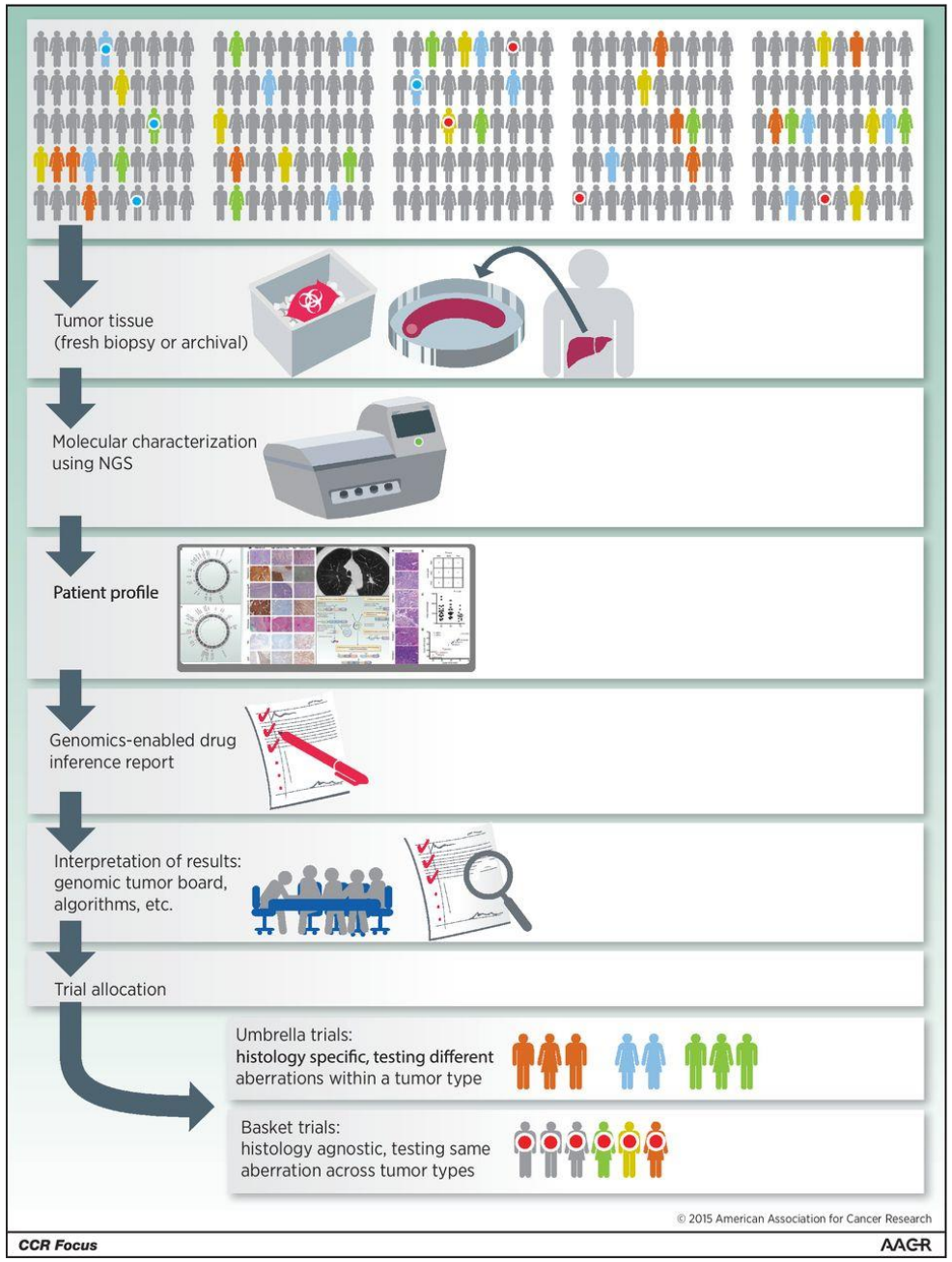

FOUNDATIONONE®CDx

PATIENT 03-2018-00006932, IT

TUMOR TYPE Unknown primary carcinoma (NOS)

REPORT DATE 26 Dec 2018

PRF# 505561

ABOUT THE TEST FoundationOne® CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

PATIENT

DISEASE Unknown primary carcinoma (NOS)
NAME 03-2018-00006932, IT
DATE OF BIRTH 21 December 1959
SEX Female
MEDICAL RECORD # Not given

PHYSICIAN

ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 501919
PATHOLOGIST

SPECIMEN

SPECIMEN SITE
SPECIMEN ID I17P000595
SPECIMEN TYPE Slide
DATE OF COLLECTION 18 November 2017
SPECIMEN RECEIVED 29 November 2018

Genomic Signatures

Tumor Mutational Burden - TMB-High (28 Muts/Mb)
Microsatellite Status - MSI-Intermediate

Gene Alterations

For a complete list of the genes assayed, please refer to the Appendix.

CD79A R131fs*61
MLH1 N168fs*4
MSH2 F58fs*27
SETD2 F1132fs*22
TP53 R175H

5 Therapies approved in the EU

0 Therapies with Lack of Response

10 Clinical Trials

Utilità incerta:

Studi clinici controllati!

Clinical Cancer Research

Lillian L. Siu et al. “Application of NGS to guide clinical trials in cancer patients” Clin Cancer Res 2015; 21:4536-4544

Siamo pronti per il test BRCA «universale»?

THE AMERICAN SOCIETY OF Breast Surgeons

Consensus Guideline on Genetic Testing for Hereditary Breast Cancer

Purpose: To outline recommendations for genetic testing that medical professionals can use to assess hereditary risk for breast cancer in their patients

Methods: Literature review included large datasets, basic science publications, and recent updated national guidelines. This is not an exhaustive systematic review, but a comprehensive review of the most impactful evidence in the modern literature on this subject. Genetic testing to assess hereditary risk of cancer is a broad and dynamic area of medical research. The focus of this guideline is limited in scope to previously put forth fi

Approval: Please see statement was develop

Recommendations:

1. **Breast surgeons, genetic counselors, and other medical professionals knowledgeable in genetic testing can provide patient education and counseling and make recommendations to their patients regarding genetic testing and arrange testing.** When the patient's history and/or test results are complex, referral to a certified genetic counselor or genetics professional may be useful. Genetic testing is increasingly provided through multi-gene panels. There are a wide variety of panels available, with different genes on different panels. There is a lack of consensus among experts regarding which genes should be tested in different clinical scenarios. There is also variation in the degree of consensus regarding the understanding of risk and appropriate clinical management of mutations in some genes.

2. **Genetic testing should be made available to all patients with a personal history of breast cancer**. Recent data support that genetic testing should be offered to each patient with breast cancer (newly diagnosed or with a personal history). If genetic testing is performed, such testing should include BRCA1/BRCA2 and PALB2, with other genes as appropriate for the clinical scenario and family history. For patients with newly diagnosed breast cancer, identification of a mutation may impact local treatment recommendations (surgery and potentially radiation) and systemic therapy. Additionally, family members may subsequently be offered testing and tailored risk reduction strategies.

Grazie per l'attenzione!