Studio del profilo molecolare del carcinoma tiroideo: come farlo

Giancarlo Pruneri

Fondazione IRCCS Istituto Nazionale Tumori

Università degli Studi Milano

Outline

- Algoritmi dei test per i pazienti con tumore della tiroide
- NGS nei laboratori di patologia
- Molecular tumor board
- Biopsia liquida
- La rete dei laboratori

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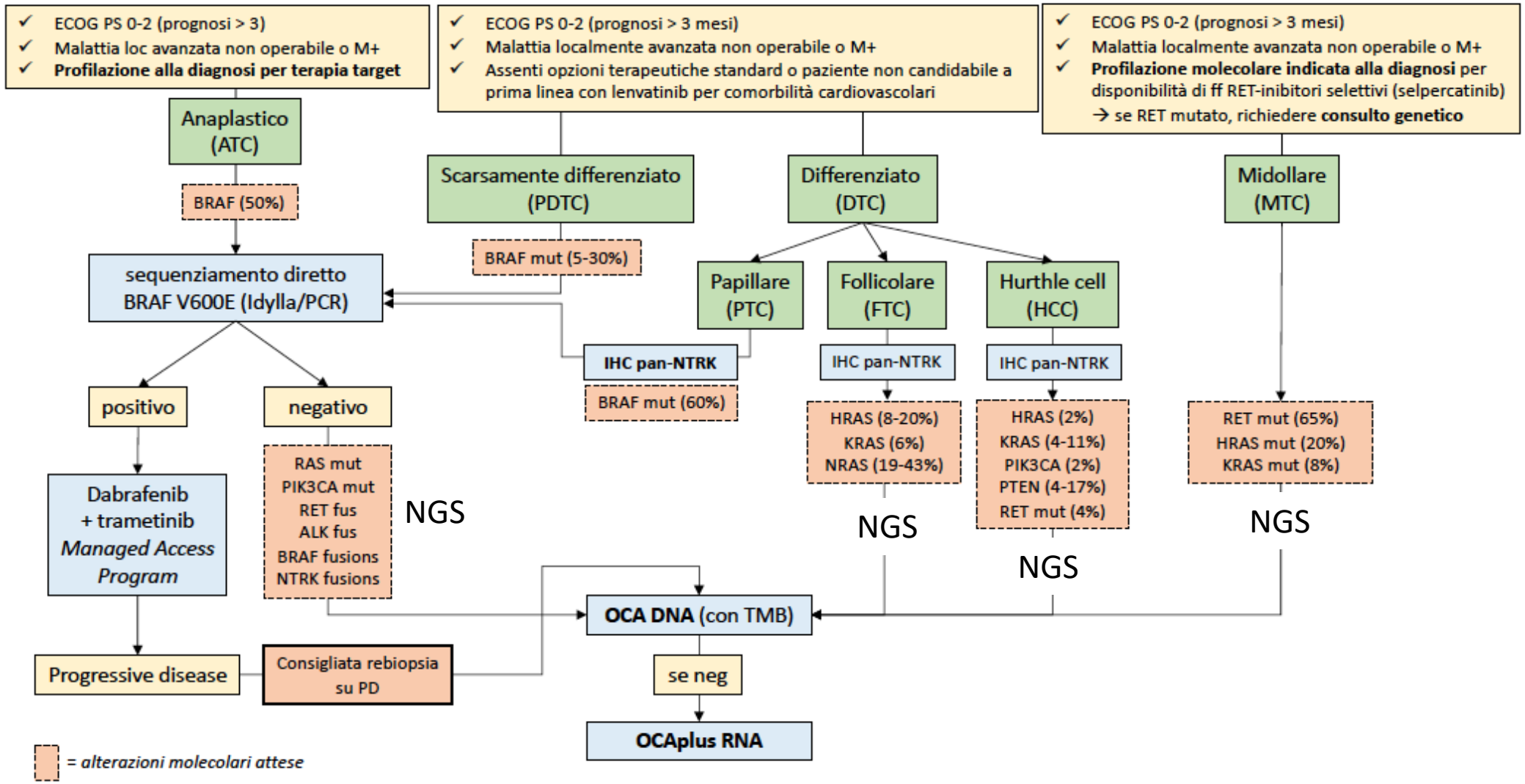
Pathology lab, tools for the analysis of predictive factors

(Multiplex) IHC
ISH, FISH
Digital Pathology (in situ transcriptomic)
RT-PCR
Gene expression
Gene sequencing
Massive parallel sequencing (NGS)
RNA-seq
Cytogenetics

Giancarlo Pruneri, MD

Profilazione carcinomi tiroidei



Courtesy Dr. Colombo

RET testing

Fusion: lung adenocarcinoma (up to 2%) and papillary thyroid carcinoma (5-10%)

Mutation: medullary thyroid carcinoma (hallmark of MEN2)

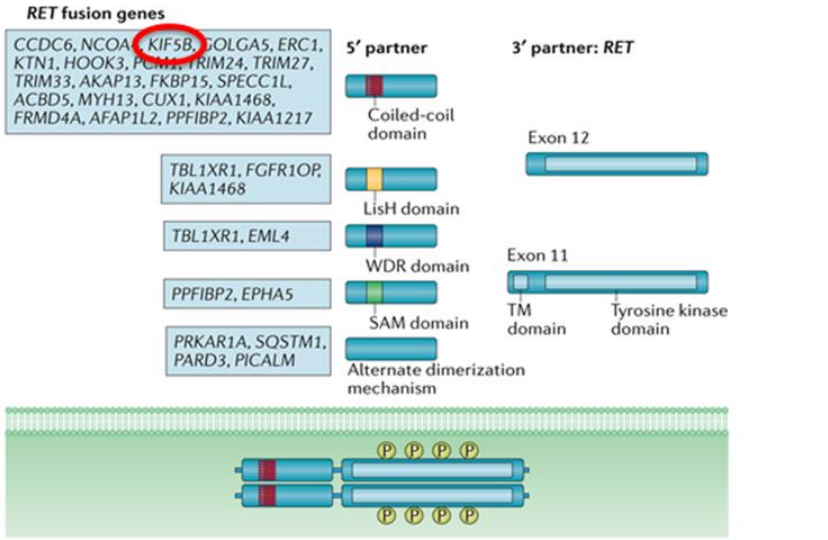
- *No validated immunoistochemistry*

Fusion:

- FISH
- RT-PCR
- NGS (DNA or **RNA** based)

Mutation:

- PCR
- NGS (DNA based)



Drilon A, et al. Nat Rev Clin Oncol. 2018 Mar;15(3):151-167

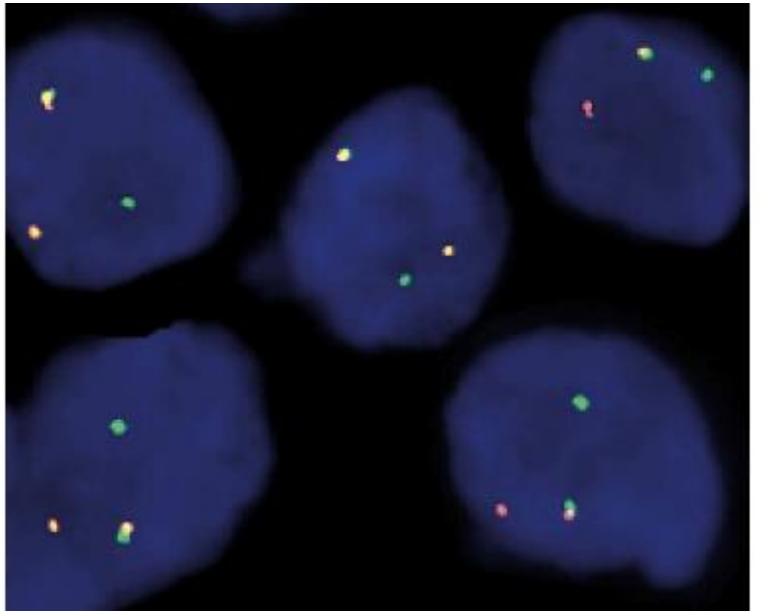
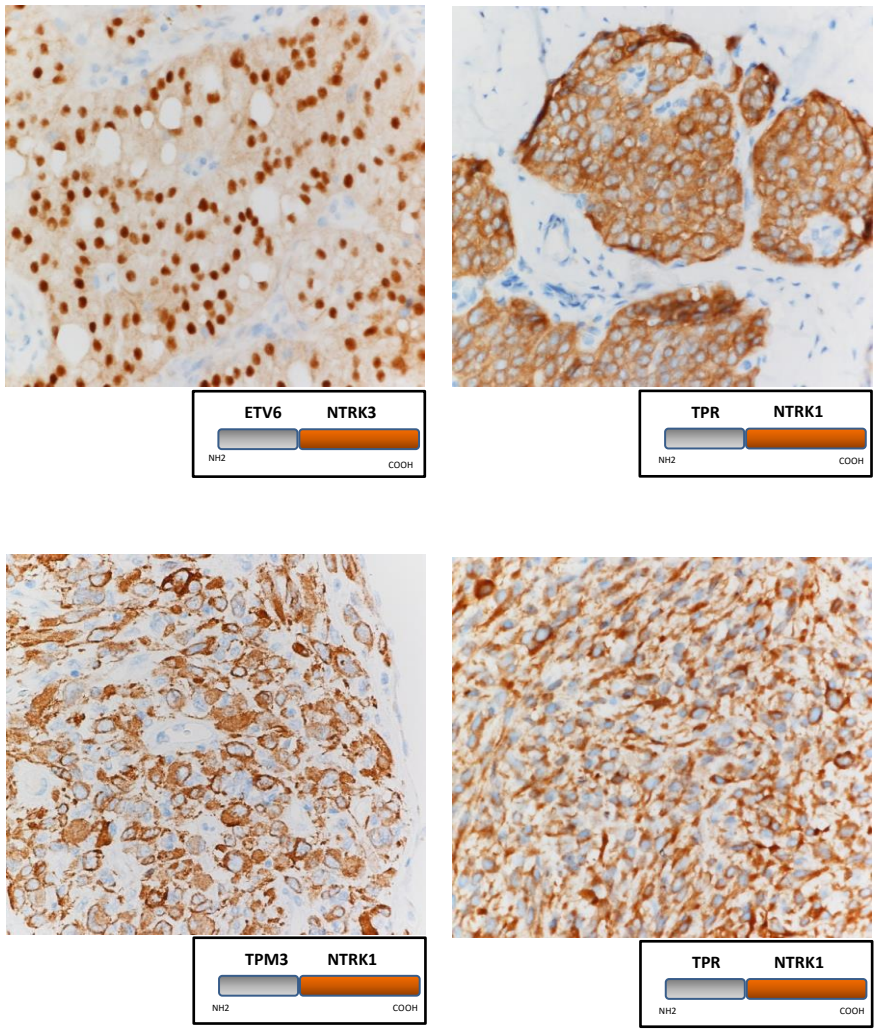


Table 1. Comparison between pan-TRK ICH and NGS data.

	Histopathological diagnosis	Immunoreactive cells (%)	Staining intensity	IHC pattern	NGS results
1	Papillary thyroid carcinoma	100	2+	C	TPR-NTRK1
2	Adenocarcinoma (parotid)	60	2+	N	ETV6-NTRK3
3	Salivary gland secretory carcinoma	100	3+	N	ETV6-NTRK3
4	NSCLC	100	1+	C	WT
5	NSCLC	30	2+	C + M	WT
6	NSCLC	60	1+	C + M	WT
7	NSCLC	15	2+	C	WT
8	NSCLC	10	2+	C	NE
9	Mucoepidermoid carcinoma (pleura)	60	1+	C	NE
10	Adenoid cistic carcinoma (nasal fossa)	20	1+	C	NE
11	Spindle cell sarcoma - lipofibromatis-like neural tumor	100	2+	C + M	TFG -NTRK3
12	NTRK-rearranged spindle cell neoplasm	100	3+	C	TPM3-NRTK1
13	NTRK-rearranged spindle cell neoplasm	100	2+	C + M	TPM3-NTRK1
14	NTRK-rearranged spindle cell neoplasm	70	2+	C	TPM3-NTRK1
15	NTRK-rearranged spindle cell neoplasm	100	3+	N	ETV6-NTRK3
16	NTRK-rearranged spindle cell neoplasm	80	2+	C	TPR-NTRK1
17	Inflammatory myofibroblastic tumor	100	3+	N	ETV6-NTRK3
18	Inflammatory myofibroblastic tumor	100	3+	N	ETV6-NTRK3
19	Mullerian adenosarcoma	100	1+	C	WT
20	Sarcoma, NOS	20	2+	C + M	WT
21	Sarcoma, NOS	50	2+	C	WT
22	Sarcoma, NOS	70	2+	C	WT
23	Follicular dendritic cell sarcoma	80	1+	C	WT
24	Endometrial stromal sarcoma	90	1+	M	WT
25	Glioma	20	2+	C	WT
26	Glioblastoma	30	2+	C	WT
27	Glioblastoma	60	2+	C	WT
27	Neuroepithelial neoplasm	20	1+	C + M	WT
29	Pilocytic astrocytoma	100	2+	C	WT
30	Pilocytic astrocytoma	20	1+	C	NE
31	Glioma	60	2+	C	WT
32	Glioma	80	1+	C	WT
33	Neuroblastoma	80	2+	C + M	WT
34	Neuroblastoma	80	2+	C + M	WT

Abbreviations. NE, not evaluable; NOS, not otherwise specified; WT, wild type; C, cytoplasmic; N, nuclear; M, membranous; 1+, mild; 2+, moderate; 3+, high staining intensity.



Vingiani, submitted

Table 2. Correlation between pan-TRK IHC and NGS results.

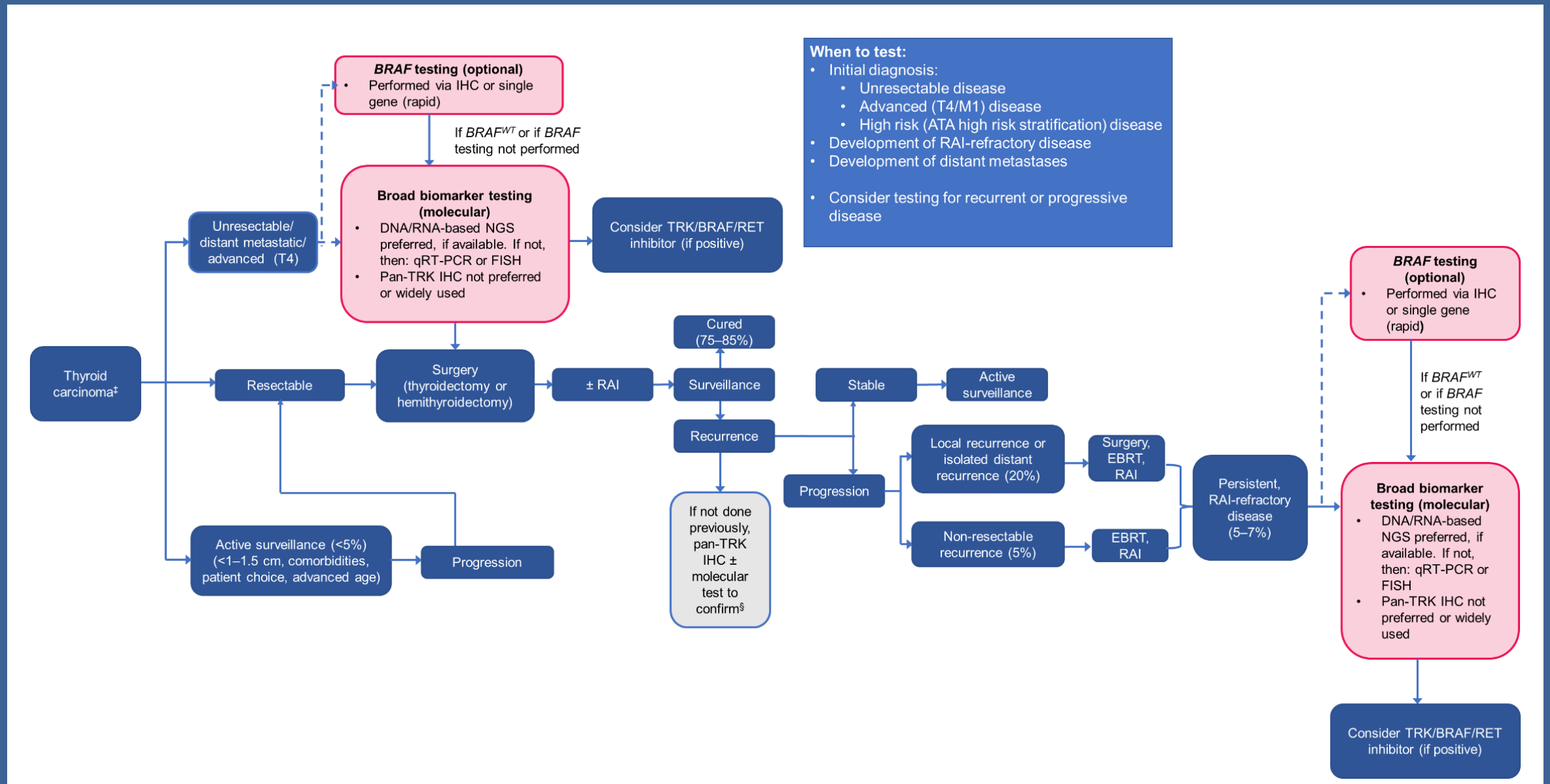
	NTRK **NGS rearranged**	***NTRK*** **NGS negative**	**Total**
Pan-TRK IHC +	11	19	**30**
Pan-TRK IHC -	1*	86	**87**
Total	**12**	**105**	**117**

*This case did not show any signal of *NTRK* gene rearrangement by FISH

Table 3. Concordance rate and predictive values of pan-TRK immunohistochemistry as related to NGS results, according to tumor type.

Histotype	**Overall Concordance Rate (%)**	**Negative Predictive Value (%)**	**Positive Predictive Value (%)**
Carcinoma	94.2	98.8	42.8
Sarcoma	68.4	100	57.1
NST*	18.2	100	0
Total	**82.9**	**98.8**	**36.7**

*NST, Nervous system tumors, including primary central nervous system tumors and neuroblastoma



Adapted from Bebb *et al* 2021

Haddad, JAMA Oncol, in press

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Table 2. Summary recommendations

Tumour types	General recommendations for daily practice	Recommendation for clinical research centres	Special considerations for patients
Lung adenocarcinoma	Tumour multigene NGS to assess level I alterations. Larger panels can be used only on the basis of specific agreements with payers taking into account the overall cost of the strategy (drug included[a]) and if they report accurate ranking of alterations. NGS can either be done on RNA or DNA, if it includes level I fusions in the panel.	It is highly recommended that clinical research centres perform multigene sequencing in the context of molecular screening programmes in order to increase access to innovative drugs and to speed up clinical research. This is particularly relevant in breast, pancreatic and hepatocellular cancers where level II–IV alterations are numerous.	Using large panels of genes could lead to few clinically meaningful responders, not detected by small panels or standard testings. In this context and outside the diseases where large panels of genes are recommended, ESMO acknowledges that a patient and a doctor could decide together to order a large panel of genes, pending no extra cost for the public health care system, and if the patient is informed about the low likelihood of benefit.
Squamous cell lung cancers	No current indication for tumour multigene NGS		
Breast cancers	No current indication for tumour multigene NGS		
Colon cancers	Multigene tumour NGS can be an alternative option to PCR if it does not result in additional cost.		
Prostate cancers	Multigene tumour NGS to assess level I alterations. Larger panels can be used only on the basis of specific agreements with payers taking into account the overall cost of the strategy and if they report accurate ranking of alterations.		
Gastric cancers	No current indication for tumour multigene NGS		
Pancreatic cancers	No current indication for tumour multigene NGS		
Hepatocellular carcinoma	No current indication for tumour multigene NGS		
Cholangiocarcinoma	Multigene tumour NGS could be recommended to assess level I alterations. Larger panels can be used only on the basis of specific agreements with payers taking into account the overall cost of the strategy (drug included[a]) and if they report accurate ranking of alterations. RNA-based NGS can be used.		
Others	Tumour multigene NGS can be used in ovarian cancers to determine somatic *BRCA1/2* mutations. In this latter case, larger panels can be used only on the basis of specific agreements with payers taking into account the overall cost of the strategy (drug included[a]) and if they report accurate ranking of alterations. Large panel NGS can be used in carcinoma of unknown primary. It is recommended to determine TMB in cervical cancer, salivary cancer, thyroid cancers, well-to-moderately differentiated neuroendocrine tumours, vulvar cancer, pending drug access (and in TMB-high endometrial and SCL cancers if anti-PD1 antibody is not available otherwise).		

Utilità delle profilazioni molecolari nei tumori rari e ultrarari HN

1. **Individuare potenziali target terapeutici** per inserimento in studi clinici, EAP, MAP/programmi a uso compassionevole

   Razionale per richiesta MTB

2. **Raffinare la comprensione dei sottotipi biologici di una stessa istologia** per individuare biomarkers prognostici/predittivi

3. **Generare ipotesi per nuovi studi con terapie targeted già approvate in altre istologie o terapie di associazione** (es. chemio-targeted, immuno-targeted)

Sequencing

In-house

- Ion AmpliSeq Cancer Hotspot Panel
- LKB1 v2 custom panel
- Oncomine BRCA Research Assay
- Oncomine Comprehensive Assay Plus
- GIST custom panel

- Archer FusionPlex Lung panel
- Archer FusionPlex Sarcoma panel

Thermofisher S5

Service

- Foundation One
- Oncotype MAP

Data Analysis: variant calling, filtering and validation

Ion Torrent Suite software

- Reads alignment, trimming and coverage analysis
- Variant calling

↓

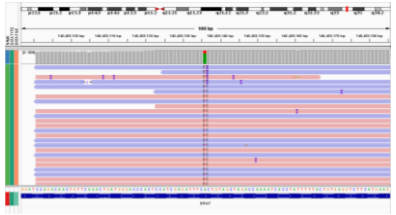
- VCF generation

↓

- Variant analysis (Open Cravat, Variant Effect Predictor)

VeP OxC

- Variant check (IGV tool, v. 2.8.13)



Archer Analysis software v 6.2
STAR-fusion
ARRIBA

Data interpretation: functional prediction and clinical annotation

- Clinical and pre-clinical evidences of altered functionality

COSMIC Catalogue Of Somatic Mutations In Cancer · gnomAD genome aggregation · varsome · ClinVar · BRCA Exchange · cBioPortal FOR CANCER GENOMICS

- In silico predictions

J. Craig Venter INSTITUTE · PROVEAN · fathmm · PolyPhen-2

- Final evaluation of pathogenicity (5-point scale)

- Assessment of clinical actionability (ESCAT Scale)

PubMed.gov · Molecular Tumor Board Portal · OncoKB · CIViC Clinical Interpretation of Variants in Cancer

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- NTRK e RET, metodi di analisi
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MTB is the tool for converting NGS data into patient care

INT
Molecular Tumor Board

MTB Chairs:
Prof. Giancarlo Pruneri
Prof. Filippo De Braud

MTB Coordinator:
Dr. Andrea Vingiani

Composition: permanent staff and delegates from MDT

ONCOLOGISTS

F. De Braud (Head)
S. Damian
M. Duca
M. Niger
C. Proto
S. Cavalieri (H&N MTD)
S. Lopez (Gyneco MTD)
C. Vernieri (Breast MTD)
A. Maurichi (Melanoma MTD)

MOLECULAR BIOLOGISTS

F. Perrone
E. Tamborini
A. Busico
E. Conca
I. Capone

MOLECULAR PATHOLOGISTS

G. Pruneri (Head)
A. Vingiani (coordinator)
F. Marra
D. Lorenzini
R. Salvatori (Resident)

CLINICAL GENETICIST

S. Manoukian
J. Azzollini

BIOINFORMATICIANS

L. Agnelli
A. De Vecchi
F. Bozzi

Data Managing Alberta Piccolo

PHARMACIST

V. Ladisa

Demographics
Clinical record

Anamnestic data

Pathological diagnosis

Mutational profile

TMB value

Therapeutic indication
Genetic counseling

NGS panel data

IRCCS Istituto Nazionale dei Tumori
Sistema Socio Sanitario Regione Lombardia
20133 - Via Venezian, 1 Milano - Tel: 02.23901
UO Multidisciplinare Gruppo MTB

Discussione Collegiale Molecular Tumor Board

Quesito diagnostico: Valutazione Terapeutica paziente non presente

Anamnesi Patologica Prossima: A seguito di comparsa di DM misto ID a Giugno 2021, con perdita di peso > 10 kg, eseguiva:
24/07/21 Ecografia addome: formazione di 43 in S6; in corrispondenza dell'ilo renale sx formazione esofitica di 23 mm
03/08/2021 RMN: al VI segmento formazione di 35 mm possibile alterazione vascolare. In sede sovrarenale sx formazione di 49 mm
03/08/2021 metanefrina U 276 (< 320), normetanefrina U 3807 (< 390), aldosterone 45.6 (< 21.4), renina 93.9 (46.1), CgA 856 (< 100), NSE, ACTH e cortisolo nei limiti.
29/09/2021 Scintigrafia MIBG: Si osserva un accumulo patologico del tracciante sola della formazione più piccola segnalata alla RM in corrispondenza del braccio mediale del surrene sinistro.
04/10/2021 Valutazione urologica specialistica (dott. Nicolai): Il quadro assume le caratteristiche di paraganglioma paraortico sottorenale e massa surrenalica coerente con adenoma non secernente.
14/12/2021 Exeresi paraganglioma sinistro videolaparoscopico e surrenectomia sinistra . EI: A) *Surrene sinistro: feocromocitoma del surrene, limitato alla ghiandola. Positività immunoistochimica per sinaptofisina, SF1, S100 (cellule sustentacolari). Mantenuta espressione immunoistochimica di SDHB. Ki-67>3%: assente. PASS SCORE: >= 4 (sec AFIP serie 4/2007). B) Paraganglioma con tessuto para-aortico sinistro: metastasi linfonodale di feocromocitoma*.

Diagnosi: Feocromocitoma surrenalico con metastasi linfonodale operato

Esito della discussione:
L'esito delle analisi molecolari riportate nel referto T22-204 eseguite mediante sequenziamento di nuova generazione è stato oggetto di discussione multidisciplinare nel contesto del Molecular Tumor Board istituzionale, in data 2022-03-17. Le alterazioni molecolari sono state valutate e classificate secondo le linee guida AMP-ASCO-CAP (Li MM et al., J Mol Diagn. 2017 Jan;19(1):4-2), con il seguente esito:

Gene	Variante cDNA	Variante aminoacidica	Classificazione	Frequenza allelica
DDX4	c.827T>C	p.Val276Ala (V276A)	VUS	52%
MAX	c.196A>T	p.Lys66Ter (K66*)	Pathogenic	63%
BLM	c.2784T>G	p.Asp928Glu (D928E)	VUS	51%
ADAT1	c.505T>G	p.Ser169Ala (S169A)	VUS	56%
RAD51D	c.775C>T	p.Arg259Trp (R649W)	VUS	39%
RET	c.1946C>T	p.Ser649Leu (S649L)	Risultati discordanti	51%
FANCF	c.1_2delAT		VUS	25%
wt	NA			

Il valore del TMB è 2.85 muts/Mbp.

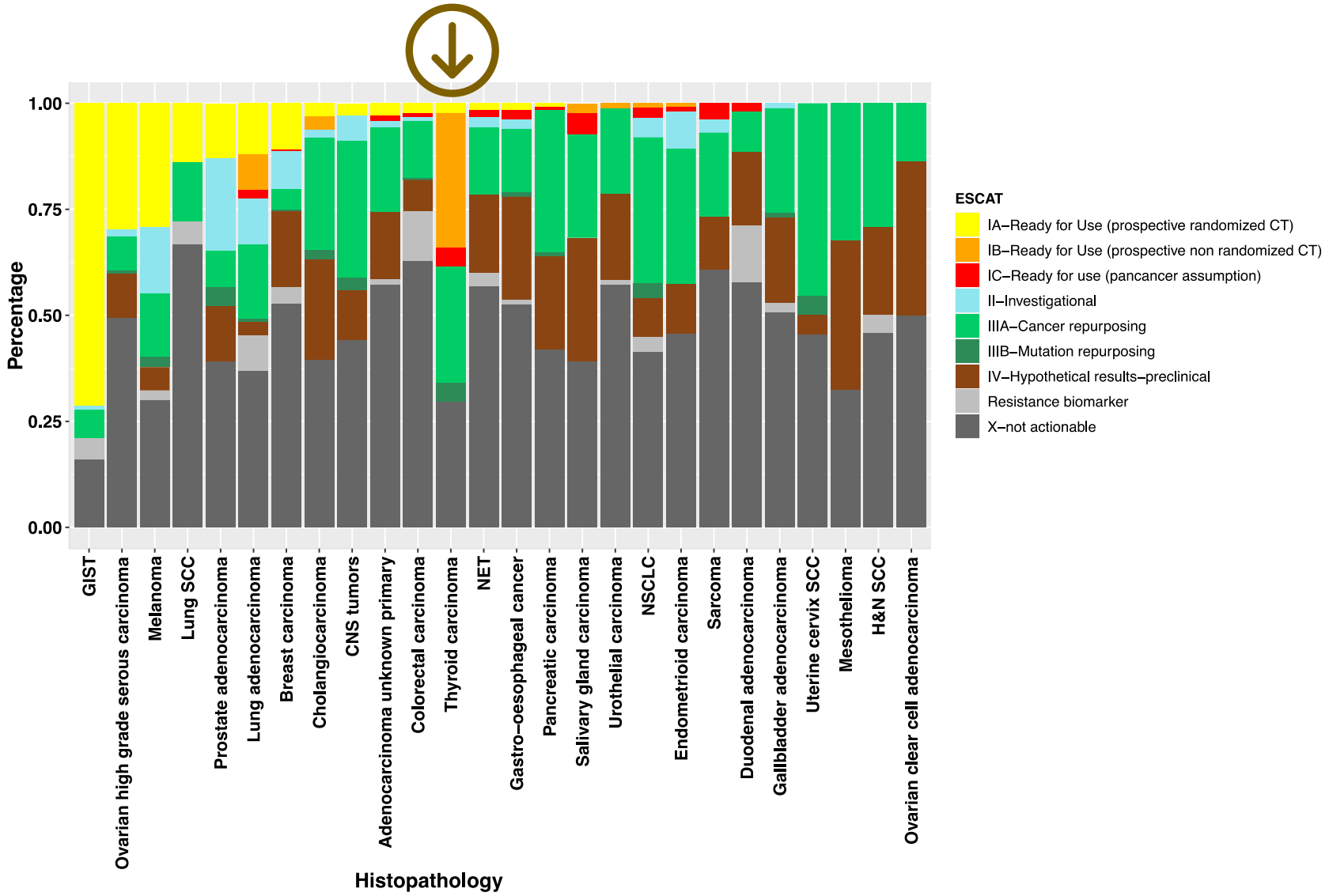
In considerazione della presenza della variante p.S649L del gene RET, per la quale sono presenti in letteratura ed in database genomici evidenze a favore di potenziale patogenicità, si segnala possibile sensibilità a Selpercatinib.
In assenza di valide alternative terapeutiche, si segnala disponibilità di protocollo INT 63/18, in fase di arruolamento presso il nostro Istituto.

In considerazione della variante K66* del gene MAX e della variante S649L del gene RET si ritiene indicata consulenza genetica.

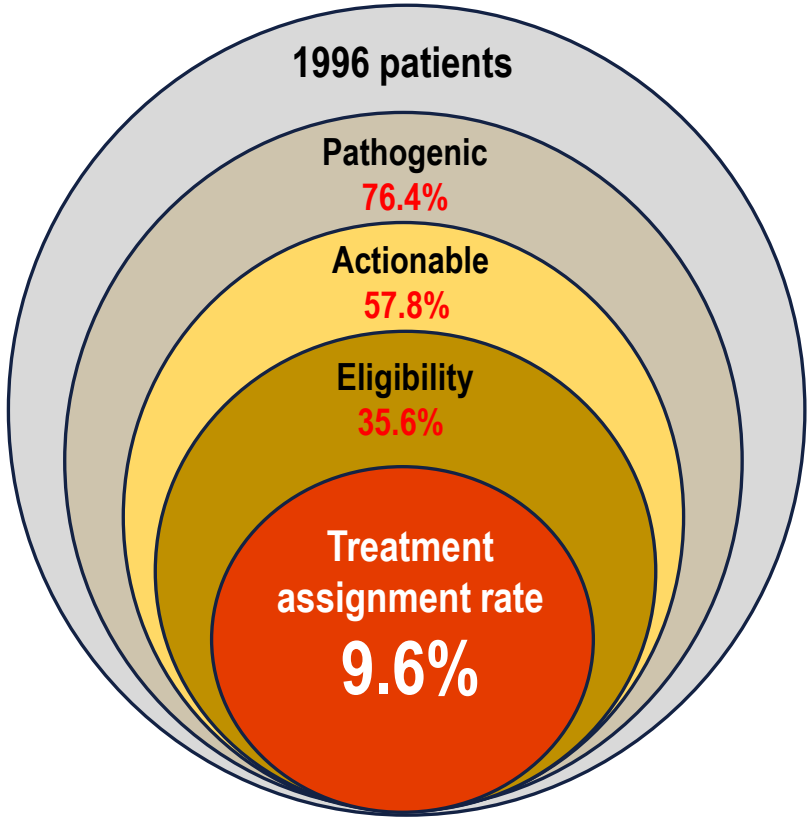
Metodica di analisi NGS.Pannello Oncomine Comprehensive Assay Plus (DNA) mediante tecnologia IonTorrent (Thermo Fisher Scientific, Life Technologies), per l'analisi delle alterazioni molecolari dei seguenti geni:

A1CF, ABCB1, ABL1, ABL2, ABRAXAS1, ACSM2B, ACVR1B, ACVR2A, ADAM18, ADAMTS12, ADAMTS2, AKT1, AKT2, AKT3, ALK, AMER1, ANO4, APC, AR, ARAF, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ARMC4, ASXL1, ASXL2, ATM, ATP1A1, ATR, ATRX, AURKA, AURKB, AURKC, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BCL2, BCL2L12, BCL6, BCOR, BCR,

ESCAT, histology



Patient treatment, INT real-world data



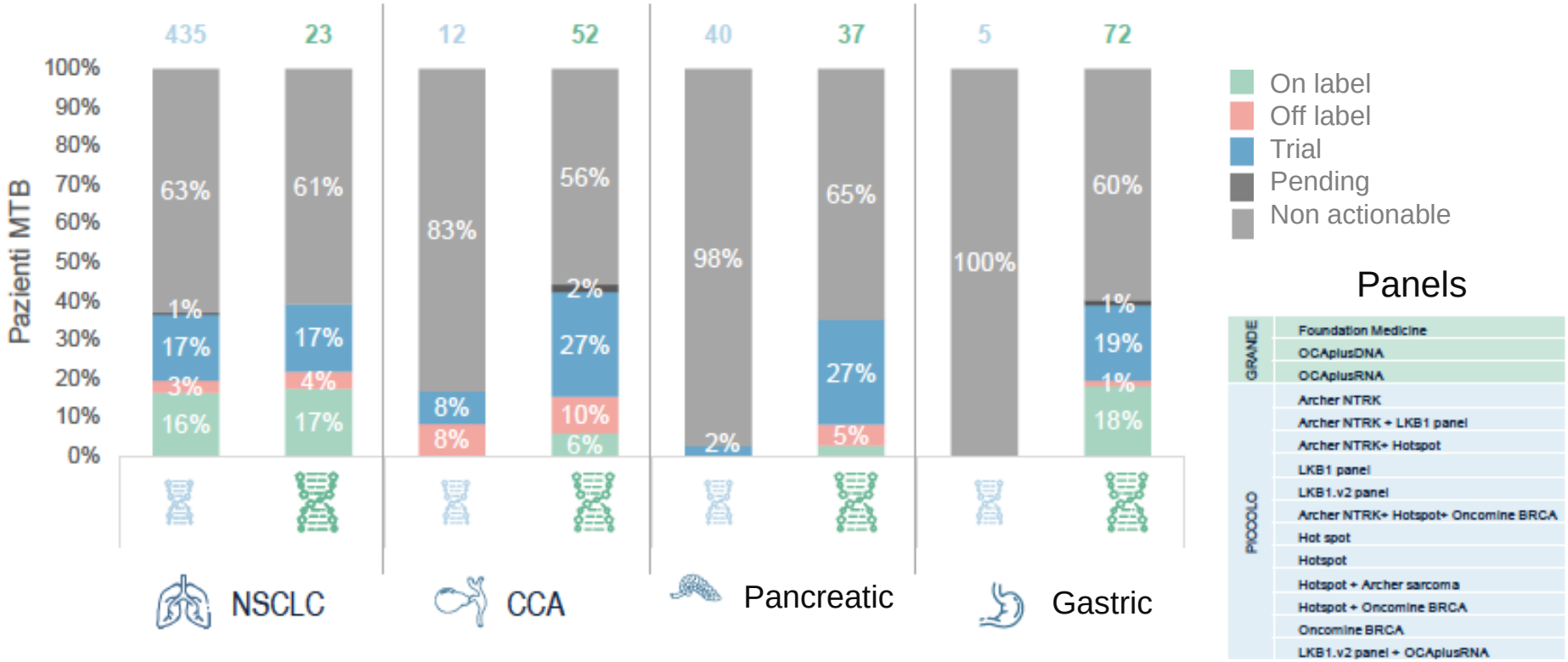
Eligibile -> treatment 26% drop

9.4% receiving standard therapy
5% targeted treatment unavailable
3.4% early-stage tumors
3.2% poor PFS, intervening death
1.4% confirming previous findings
6.6% others

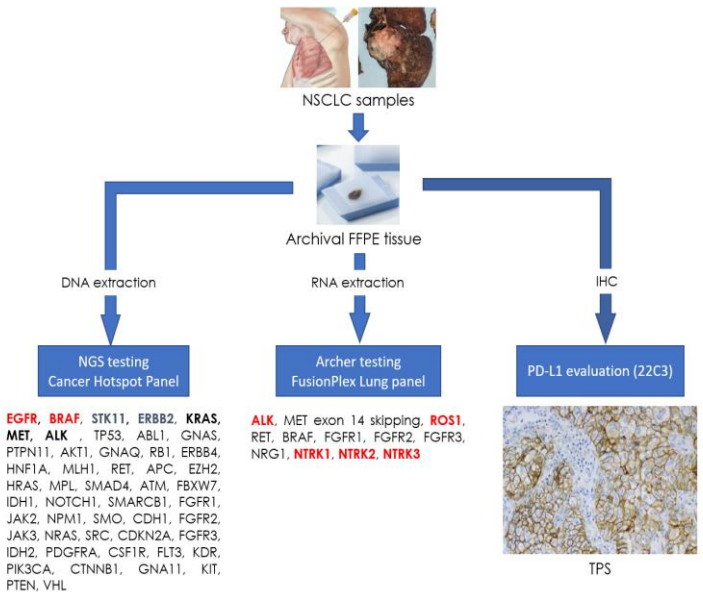
30% clinical trials

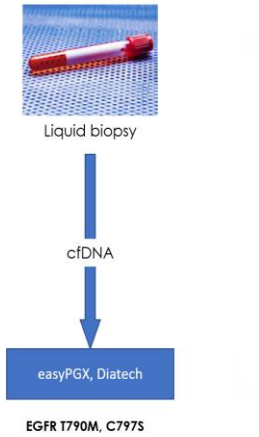
NCI MATCH **2.5%-17.8%** (Letai, Nat Med, 2017, Flaherty JCO 2020)
ProfiLER **6%** (Tredan Ann Oncol 2019)

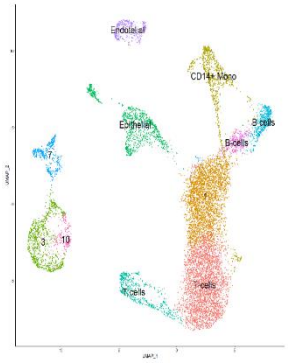
Eleggibilità rispetto all'ampiezza dei pannelli genici



Leveraging genomic and transcriptomic for patient care and translational research
First patient Jan 1, 2022 up to 2,500 pts/year







Comprehensive capture-based targeted NGS panels (~ 500 genes) Hybrid DNA -RNA

Targeted NGS panels

Germline targeted NGS

Bulk-RNA seq and Single cell sequencing

BRCA, mut tumor load, MSI, copy number

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

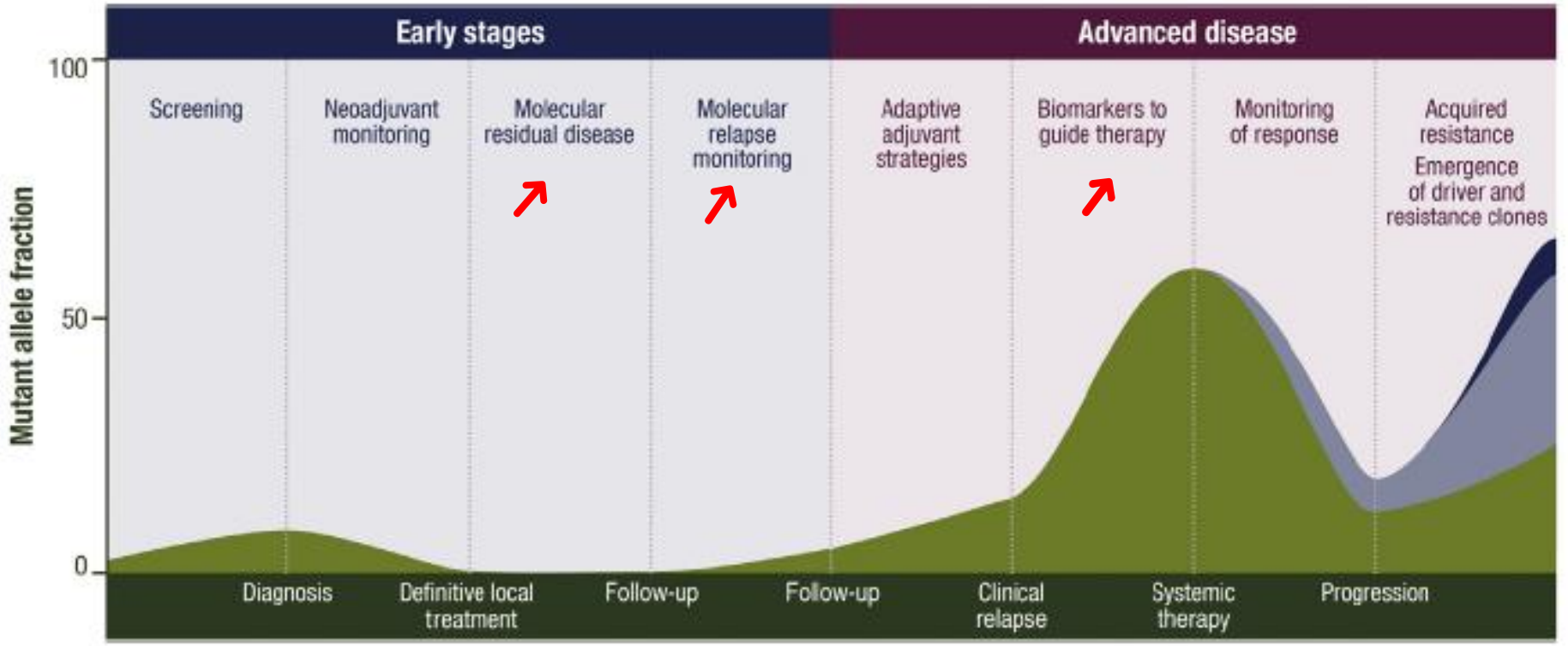
ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

https://doi.org/10.1016/j.annonc.2022.05.520

ESMO recommendations on the use of circulating tumour DNA assays for patients with cancer: a report from the ESMO Precision Medicine Working Group

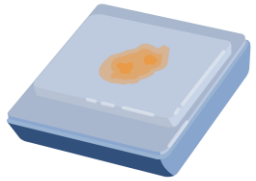
J. Pascual[1], G. Attard[2], F.-C. Bidard[3,4], G. Curigliano[5,6], L. De Mattos-Arruda[7,8], M. Diehn[9], A. Italiano[10,11,12], J. Lindberg[13], J. D. Merker[14], C. Montagut[15], N. Normanno[16], K. Pantel[17], G. Pentheroudakis[18], S. Popat[19,20], J. S. Reis-Filho[21], J. Tie[22,23], J. Seoane[24,25], N. Tarazona[26,27], T. Yoshino[28] & N. C. Turner[19,20*]



Applications: advanced cancer genotyping

- Alternative option to tissue genotyping (aggressive tumour types, tissue biopsy unavailable or inappropriate)
- Collected when cancer is progressing, either treatment naive or after prior lines of therapy
- Choice between RT-PCR, digital PCR and NGS assays in a clinical practice setting defined by availability, reimbursement status and number of tier I actionable genetic aberrations
- Caution in interpretation of pathogenic variants in high penetrance cancer susceptibility genes (such as BRCA1, BRCA2, PALB2) -> validated germline testing should be carried out to confirm germline or somatic nature
- ctDNA assays have lower sensitivity for detection fusions and copy number events
- All oncology physicians should have access to a molecular tumour board, for education early in use to ensurecorrect interpretation of results, and for discussion of difficult cases to ensure appropriate decisions are made

TSO 500



Assay	TruSight Oncology 500				
System	NextSeq 550 or NextSeq 550Dx[a]	NovaSeq 6000 System			
Flow cell	High-output	SP	S1	S2	S4
No. samples	8	16	32	72	192

a. NextSeq 550Dx System in Research Mode

TSO 500 ctDNA

	TruSight Oncology 500	TruSight Oncology 500 ctDNA
Cancer Type	Pan-Cancer	Pan-Cancer
Content Specifications	Targeted selection of DNA from 523 genes of interest, and RNA from 55 genes, for a total of 1.94Mb panel size. • Guideline Coverage: Broad coverage of key guidelines for multiple solid tumor types • Clinical Trials Coverage: Over 1,000 clinical trials • Immuno-oncology Biomarker Coverage: Biomarkers TMB and MSI included; also inclusive of HLA regions, POLE1 and POLD1*. • TruSight Oncology 500 HRD** kit content includes coverage of ~25,000 SNP's to assess homologous recombination deficiency through a comprehensive genomic instability score (LOH+TAI+LST), powered by Myriad Genetics. • TruSight Oncology 500 HRD** is an optional add-on kit to TruSight Oncology 500. **Not available in the US or Japan	Targeted selection of 523 genes (full coding sequence) for a total of 1.94Mb panel size. • Guideline Coverage: Broad coverage of key guidelines for multiple solid tumor types • Immuno-oncology Biomarker Coverage: TMB and MSI*
Hands-On Time	Manual: ~10.5 hrs Automated: ~2.5 hrs (TruSight Oncology 500 only)	Manual: ~10.5 hrs Automated: N/A
Input Quantity	40 ng DNA, 40 ng RNA	30 ng cfDNA (8-10 ml of plasma)
Method	Target Enrichment, Target Enrichment, Targeted DNA Sequencing, Targeted RNA Sequencing	Target Enrichment, Target Enrichment, Targeted DNA Sequencing
Nucleic Acid Type	RNA, DNA	DNA
Specialized Sample Types	FFPE Tissue	Blood, Circulating Tumor DNA
Species Category	Human	Human
System Compatibility	NextSeq 500, NextSeq 550, NextSeq 550Dx in Research Mode	NovaSeq 6000
Technology	Sequencing	Sequencing
Variant Class	Copy Number Variants (CNVs), Gene Fusions, Insertions-Deletions (indels), Single Nucleotide Variants (SNVs), Transcript Variants	Copy Number Variants (CNVs), Gene Fusions, Insertions-Deletions (indels), Single Nucleotide Variants (SNVs), Somatic Variants

Recommended Number of Samples	
24 samples per run (S4 flow cell), 800M paired-end reads	35,000x
8 samples per run (S2 flow cell), 800M paired-end reads	35,000x

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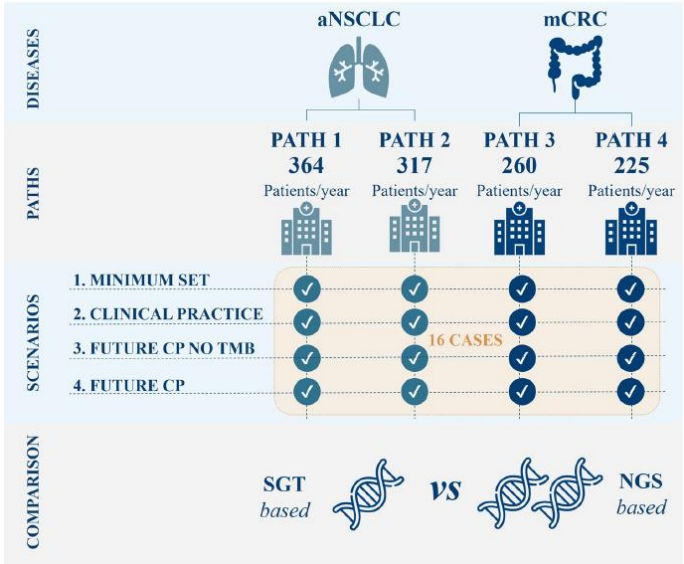
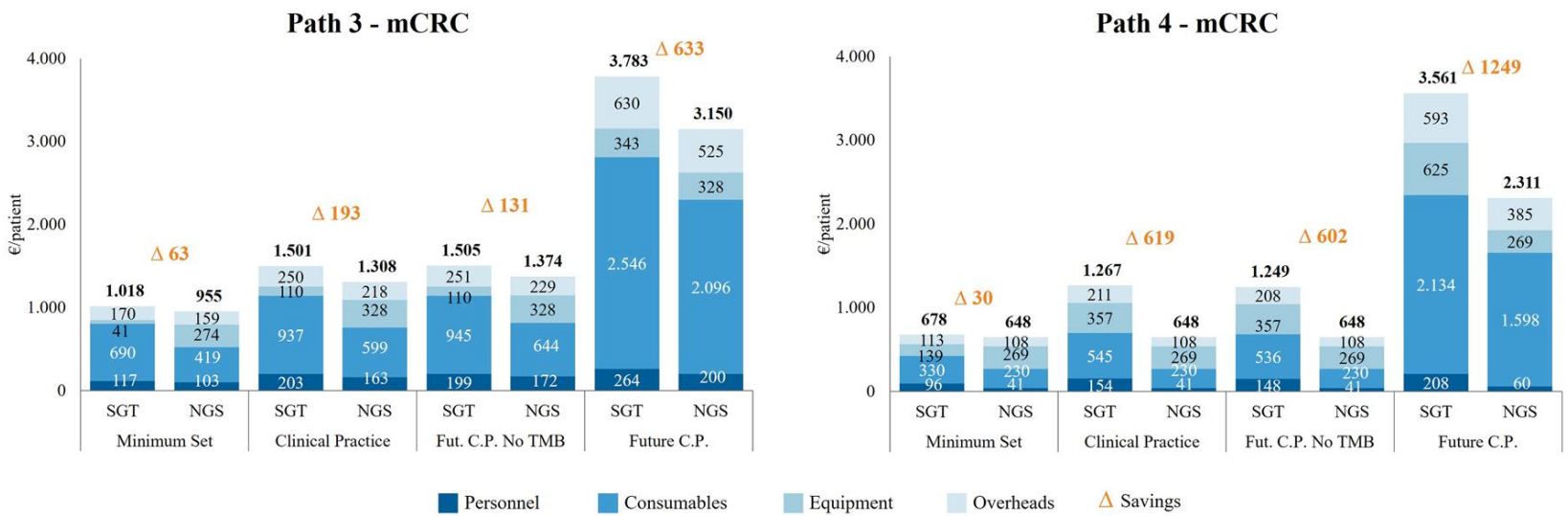
Sequenziamento genico con tecnologia NGS

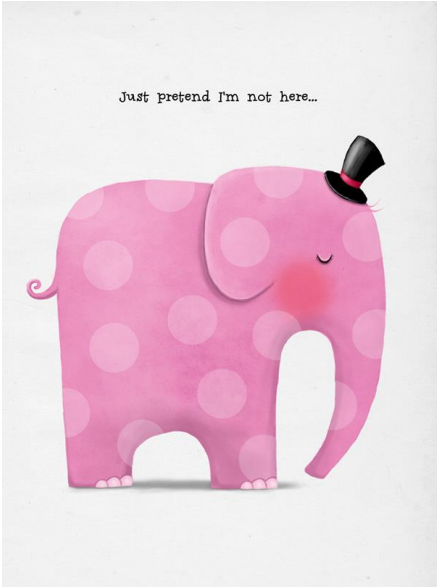


Mean cost per patient



Pruneri, Paharmacoecon Open, 2021

Ensuring equitable and efficient deployment of precision medicine is a global challenge



38,000 patients with stage IV NSCLC diagnosed between 2010 and 2018 (guidelines recommended EGFR, ALK, and ROS1 - 22% tested and only 3% treated[1]

2017 NCI survey, reasons for not ordering NGS tests: hurdles in obtaining enough tissue for testing; insufficient time to order or review tests; and (less often) lack of expert personnel to assist in test interpretation[2]

[1]Behera M, Joseph G, Rupji M, et al. Molecular testing and patterns of treatment in patients with NSCLC: an IASLC analysis of ASCO CancerLinQ Discovery Data. In: Proceedings and Abstracts of the 2022 American Society of Clinical Oncology Annual Meeting, June 3–7, 2022. Chicago: American Society of Clinical Oncology, 2022. abstract; [2]Roberts MC, Spees LP, Freedman AN, et al. Oncologist-reported reasons for not ordering multimarker tumor panels: results from a nationally representative survey. JCO Precis Oncol 2021; 5: PO.20.00431

The Lancet Oncology Commission

Lancet Oncol 2023; 24: e11–56

European Groundshot—addressing Europe's cancer research challenges: a *Lancet Oncology* Commission

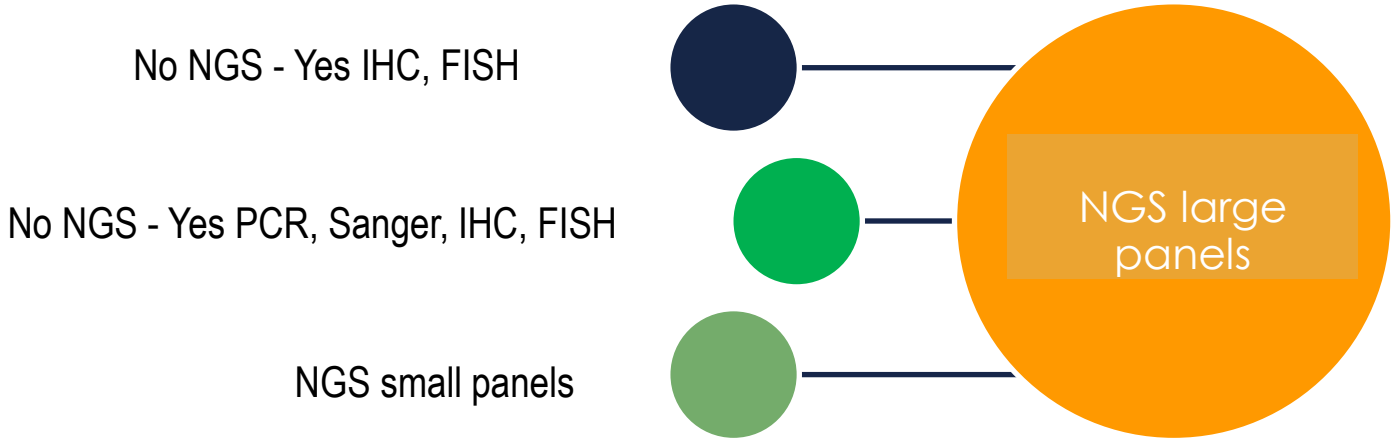
Mark Lawler, Lynne Davies, Simon Oberst, Kathy Oliver, Alexander Eggermont, Anna Schmutz, Carlo La Vecchia, Claudia Allemani, Yolande Lievens, Peter Naredi, Tanja Cufer, Ajay Aggarwal, Matti Aapro, Kathi Apostolidis, Anne-Marie Baird, Fatima Cardoso, Andreas Charalambous, Michel P Coleman, Alberto Costa, Mirjam Crul, Csaba L Dégi, Federica Di Nicolantonio, Sema Erdem, Marius Geanta, Jan Geissler, Jacek Jassem, Beata Jagielska, Bengt Jonsson, Daniel Kelly, Olaf Kelm, Teodora Kolarova, Tezer Kutluk, Grant Lewison, Françoise Meunier, Jana Pelouchova, Thierry Philip, Richard Price, Beate Rau, Isabel T Rubio, Peter Selby, Maja Južnič Sotlar, Gilliosa Spurrier-Bernard, Jolanda C van Hoeve, Eduard Vrdoljak, Willien Westerhuis, Urszula Wojciechowska, Richard Sullivan

A robust cancer biomarker infrastructure must be embedded across health systems, to ensure their deployment as innovation drivers across Europe

Embedding cancer biomarkers within real-world oncology delivery and providing genomic testing across Europe, while ensuring that inequity gaps for patients are narrowed and not widened, must be the goal

If deployed appropriately, cancer biomarkers can reduce costs by ensuring the right treatment, for the right patient, at the right dose, at the right time. Using cancer biomarkers can avoid specific cancer treatment sequelae for patients who gain no therapeutic benefit from these treatments

The last mile: towards a full coverage of diagnosis and care for *all* patients



- Many labs, one/few molecular tumor board
- Prospectively annotated database
- Biobank
- Data intellectual property
- Regional governement/AIFA/Ministry of Health and Research
- Funding
- Education

Giancarlo Pruneri, MD

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A. Vingiani, MD

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Group Leader
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Rotor gene, Quiagen
Sanger sequencing
Pyrosequencing
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1 Ion Torrent PGM, TF

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FACS, BD CANTOII
FACS, Lyric

22 contratti >700k/year

Lab technicians

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- D. Penso
- ML. Moiraghi
- M. Marcuzzo
- R. Carminati
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- A. Di Prima
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