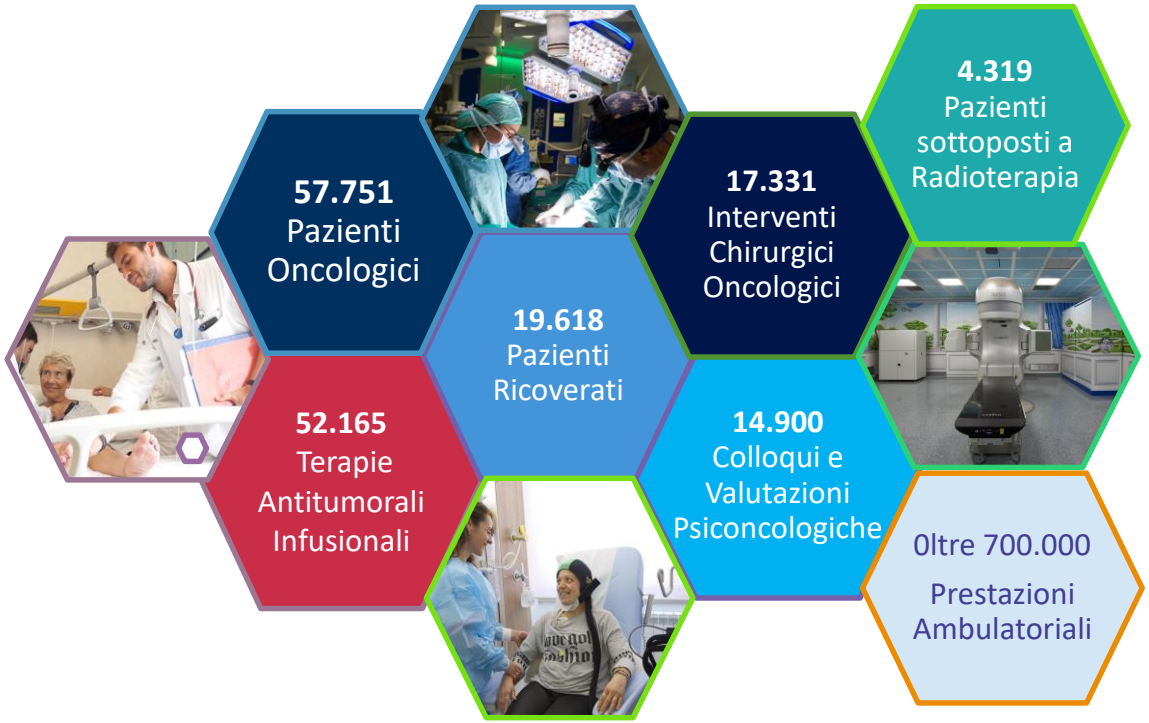
Comprehensive Cancer Center

Fondazione Policlinico Universitario A. Gemelli
Università Cattolica del Sacro Cuore

Fatti e numeri del CCC nel 2023



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 0: 1–8, 2018
doi:10.1093/annonc/mdy263

SPECIAL ARTICLE

A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)

J. Mateo[1], D. Chakravarty[2], R. Dienstmann[1], S. Jezdic[3], A. Gonzalez-Perez[4], N. Lopez-Bigas[4,5], C. K. Y. Ng[6], P. L. Bedard[7], G. Tortora[8,9], J. -Y. Douillard[3], E. M. Van Allen[10], N. Schultz[2], C. Swanton[11], F. André[12*] & L. Pusztai[13]

	Readiness for use in clinical practice	Current examples of genomic alterations
Tier I (I-A, I-B, I-C)	Targets ready for implementation in routine clinical decisions	HER2 in breast cancer BRCA1/2 in ovarian and breast cancer EGFR, ROS1/ALK in NSCLC TRK, PD1 in multiple cancers BRAF in metastatic melanoma
Tier II (II-A, II-B)	Investigational targets likely to define patients who benefit from a targeted drug, but additional data needed	PTEN pathway (PIK3CA, AKT1)
Tier III (III-A, III-B)	Clinical benefit previously demonstrated in other tumour type or for similar molecular targets	BRAF in non-melanoma cancers PALB2 and other non-BRCA DNA repair mutations
Tier IV (IVA, IVB)	Preclinical evidence of actionability	Hypothetical targets for future clinical testing
Tier V	Evidence supporting co-targeting approaches	PIK3CA in ER+, HER- breast cancer
Tier X	Lack of evidence for actionability	

NSCLC= non-small cell lung cancer

ESMO recommendations for NGS testing in solid tumors

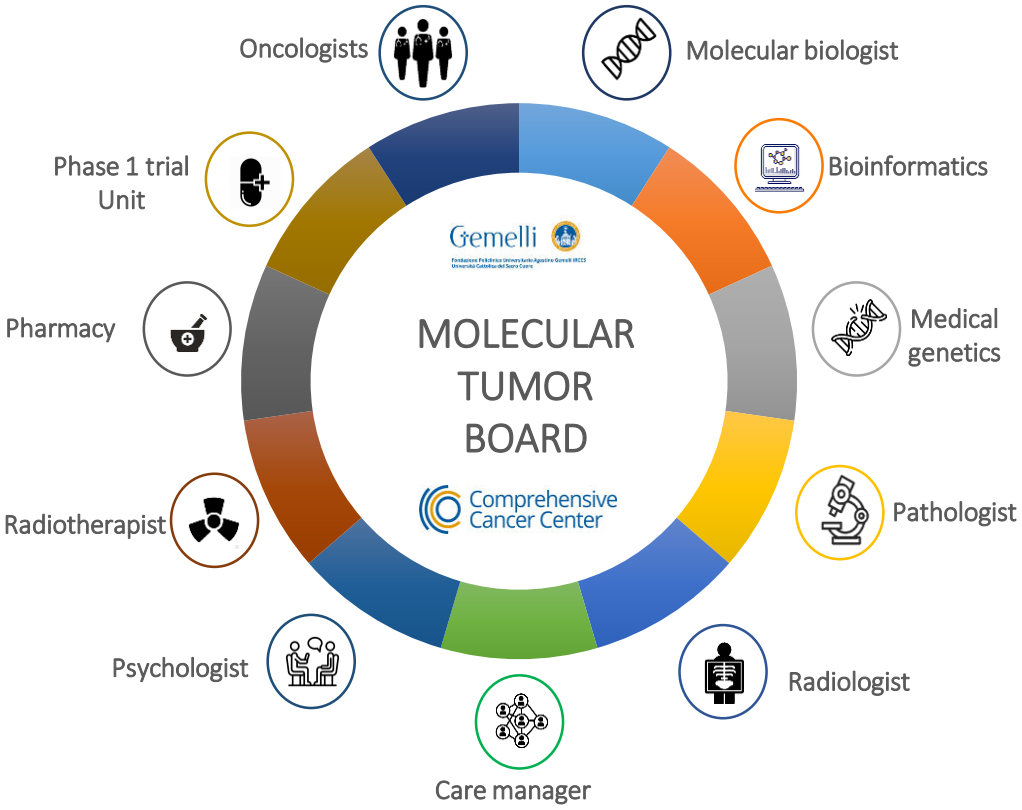
Tumour types	General recommendations for daily practice	Recommendation for clinical research centers	Special considerations for patients
Lung adenocarcinoma	Tumour multigene NGS to assess level I alterations. Larger panels are acceptable if they induce acceptable incremental costs (drug included*) and report accurate ranking of alterations. NGS can either be done on RNA or DNA, if it includes level I fusions.	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 panel 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 extracost for the public healthcare system, and if the patients 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 NGS can be an alternative to PCR if it has no additional cost.		
Prostate cancers	Multigene tumour NGS to assess level I alterations. Larger panels are acceptable if they induce only acceptable incremental costs (drug included*) and 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 are acceptable if they induce only acceptable incremental costs (drug included*) and 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. Large panels are acceptable if they do not induce extra costs (drug included*) and 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).		

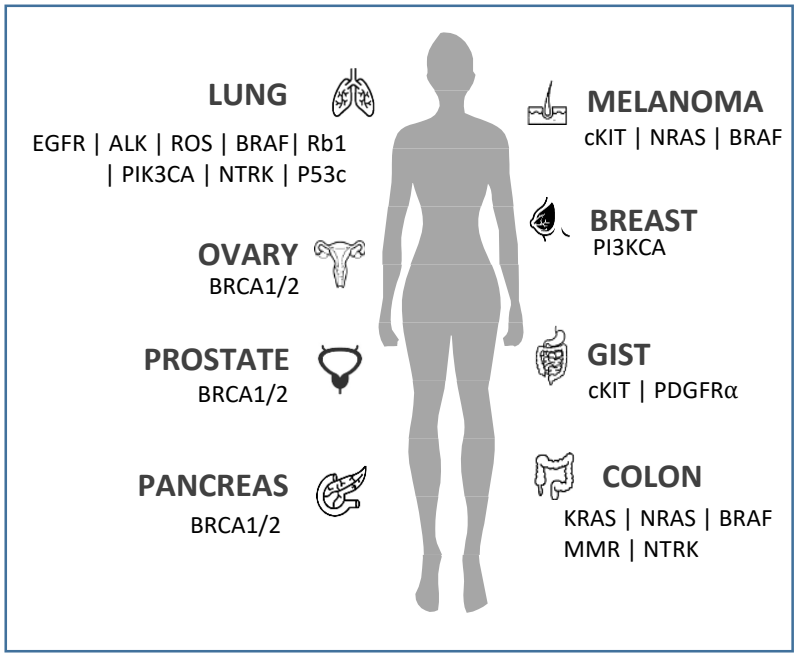
Mosele et al. Ann Oncol 2020

Tumor Board Molecolare e Profilazione Genomica

Legata al Progetto *FPG500*

Incontri il Martedì alle 13:00 ogni 2 settimane





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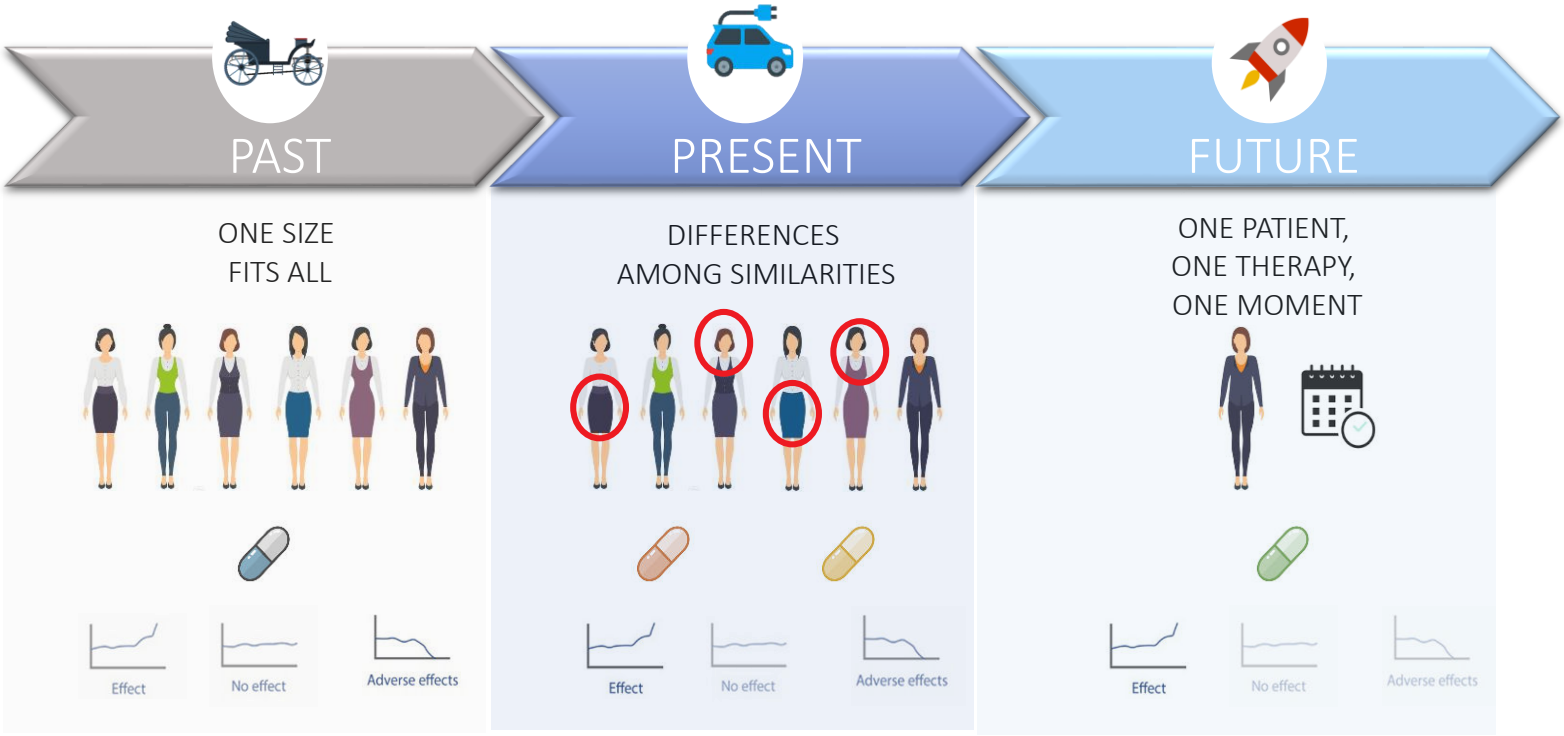
MOLECULAR TUMOR BOARD

Towards precision and personalized medicine



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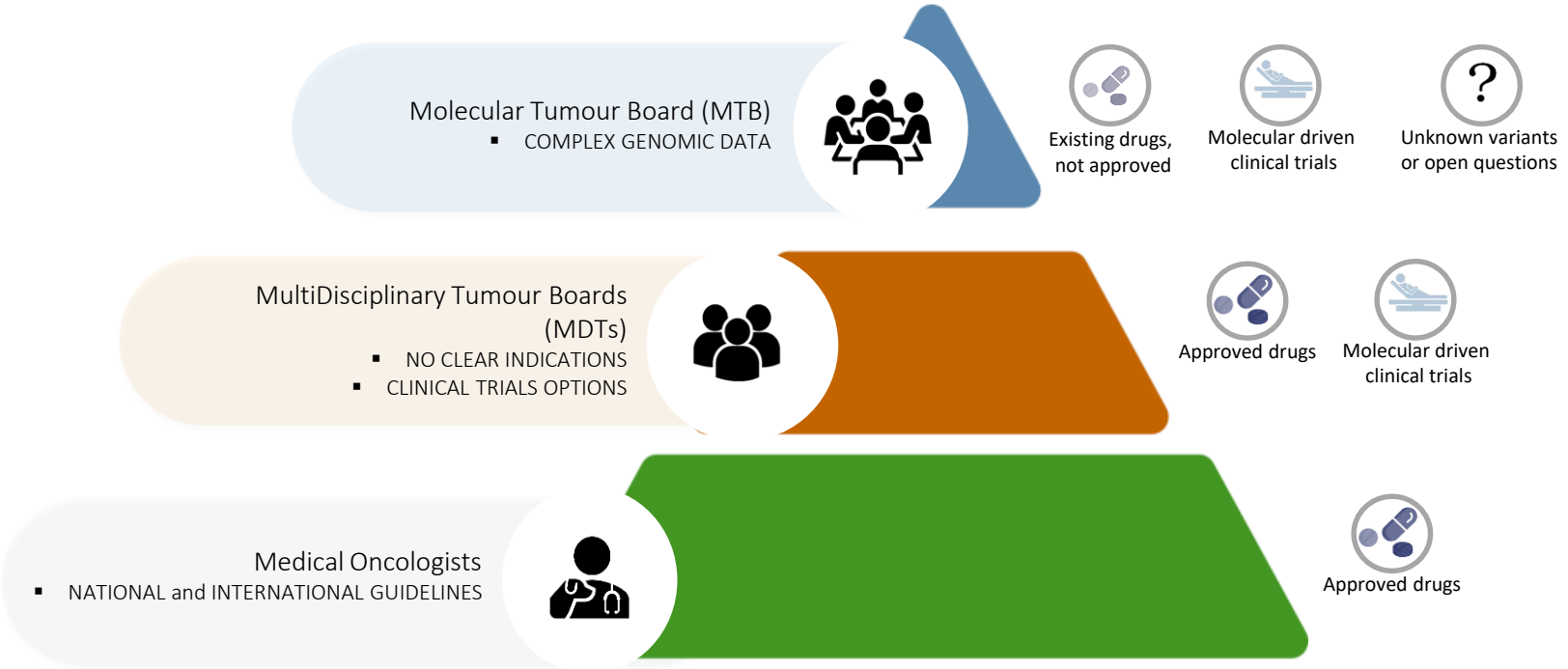
Definition and requirements: support treating physicians



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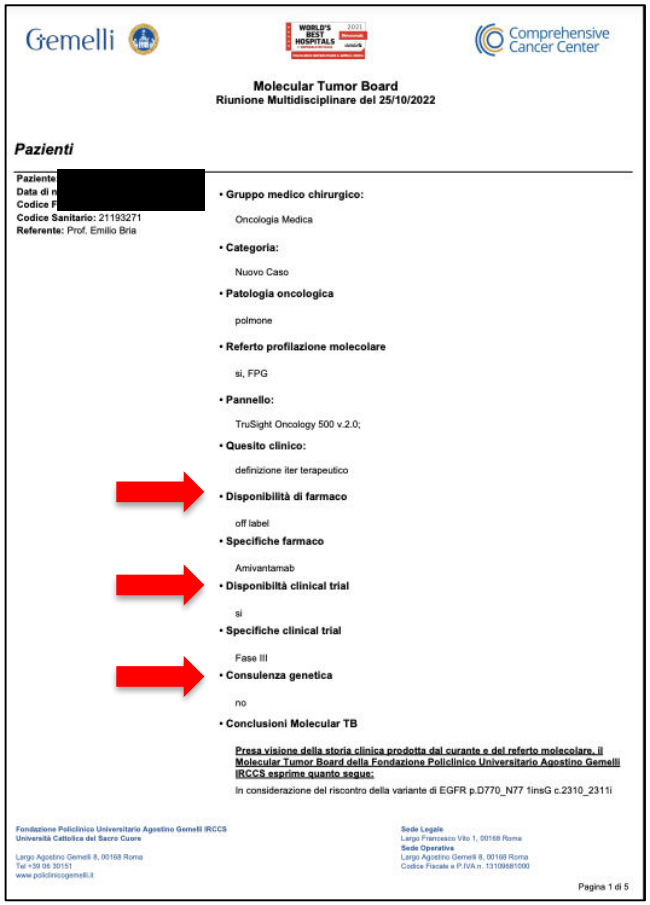
Recommendation



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Molecular Tumor Board
Riunione Multidisciplinare del 25/10/2022

Pazienti

Paziente [redacted]
Data di n
Codice F
Codice Sanitario: 21193271
Referente: Prof. Emilio Bria

- **Gruppo medico chirurgico:**
  Oncologia Medica
- **Categoria:**
  Nuovo Caso
- **Patologia oncologica**
  polmone
- **Referto profilazione molecolare**
  si, FPG
- **Pannello:**
  TruSight Oncology 500 v.2.0;
- **Quesito clinico:**
  definizione iter terapeutico
- **Disponibilità di farmaco**
  off label
- **Specifiche farmaco**
  Amivantamab
- **Disponibiltà clinical trial**
  si
- **Specifiche clinical trial**
  Fase III
- **Consulenza genetica**
  no
- **Conclusioni Molecular TB**

Presa visione della storia clinica prodotta dal curante e del referto molecolare, il Molecular Tumor Board della Fondazione Policlinico Universitario Agostino Gemelli IRCCS esprime quanto segue:

In considerazione del riscontro della variante di EGFR p.D770_N77 1insG c.2310_2311i

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore
Largo Agostino Gemelli 8, 00168 Roma
Tel +39 06 30151
www.policlinicogemelli.it

Sede Legale
Largo Francesco Vito 1, 00168 Roma
Sede Operativa
Largo Agostino Gemelli 8, 00168 Roma
Codice Fiscale e P.IVA n. 13109681000

Pagina 1 di 5

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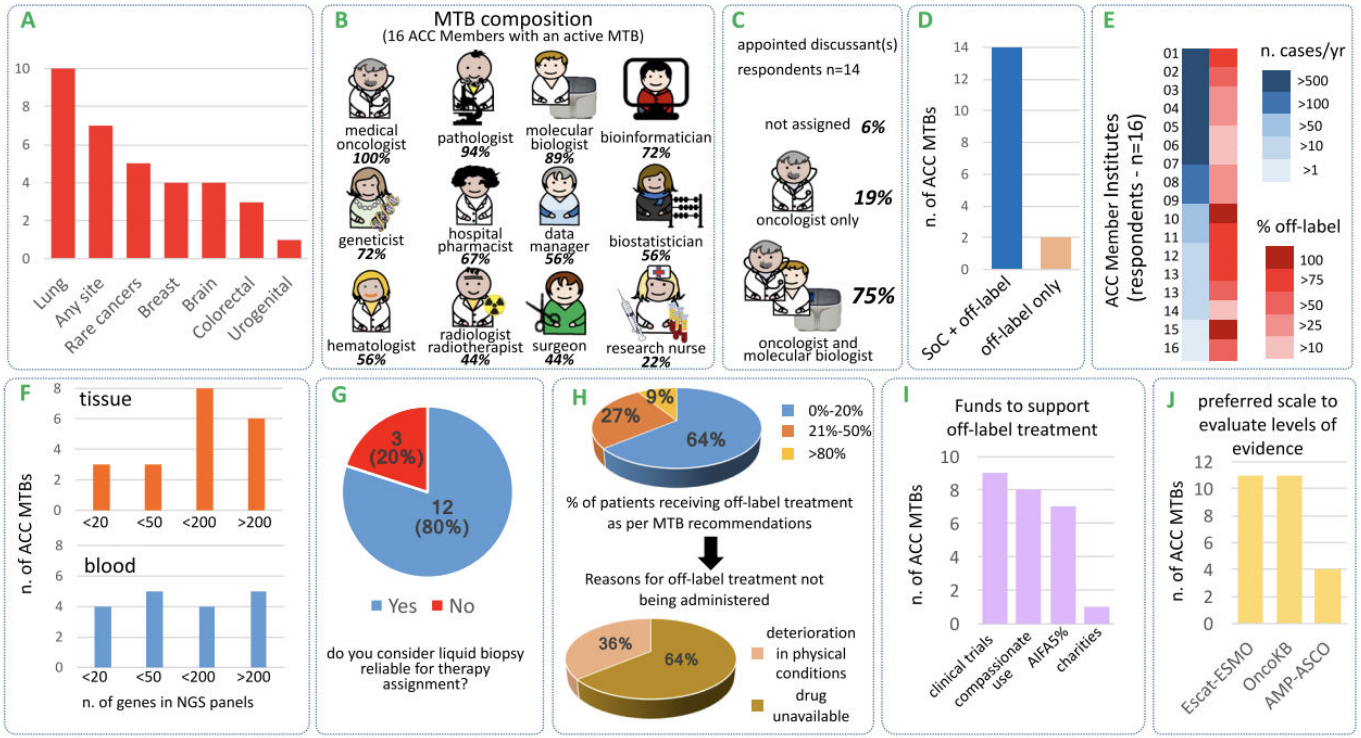
Italian survey within ACC network



Ciliberto et al. J Exp Clin Cancer Res (2022)

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Fondazione Policlinico Universitario Agostino Gemelli IRCCS internal pathway

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METHODS

Eligibility

TUMOR TYPE	TARGET	SETTING
Breast	PIK3CA	Hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer after disease progression following endocrine therapy as monotherapy
Lung	EGFR	Metastatic
	ALK	Metastatic
	ROS1	Metastatic
	BRAF	Metastatic
	NTRK	Metastatic
	RET	Metastatic
Ovary	BRCA 1/2	All patients with non-mucinous and non-borderline ovarian, fallopian tube or primary peritoneal cancer
Pancreas	BRCA 1/2	Metastatic
	NTRK	Metastatic
Prostate	BRCA 1/2	Metastatic castration resistant
Melanoma	BRAF	Metastatic or not resectable
		Resected Stage III
GIST	c-kit	Locally advanced or Metastatic
		Resected (Adjuvant)
	PDGFRα	Locally advanced or Metastatic
Colorectal	KRAS	Metastatic
	NRAS	Metastatic
	BRAF	Metastatic
	NTRK	Metastatic
Thyroid	RET	Advanced medullary thyroid cancer
		Advanced non medullary thyroid cancer
Endometrium	POLE	Stage FIGO I-II, any histotype

Il progetto FPG500

- Microlab STAR-Hamilton per la preparazione automatizzata delle librerie e Illumina™ Novaseq6000 per il sequenziamento.
- Profiling eseguito da TruSight Oncology 500 ad alta produttività (TSO500HT, Illumina) (DNA o RNA ≥ 40 ng).
- I campioni al di sotto della quantità richiesta per TSO500HT e per i quali non sono disponibili altri prelievi vengono sottoposti al test Oncomine Focus (Thermofisher) per il DNA e al pannello FusionPlex Lung di Archer per la valutazione dell'RNA.
- I campioni < 20 ng di DNA/RNA sono discussi per una nuova biopsia o test con tecniche standard (per biomarcatori approvati per la pratica clinica inclusi nei LEA) - La biopsia liquida si considera se non sono disponibili altre opzioni.

Il progetto FPG500

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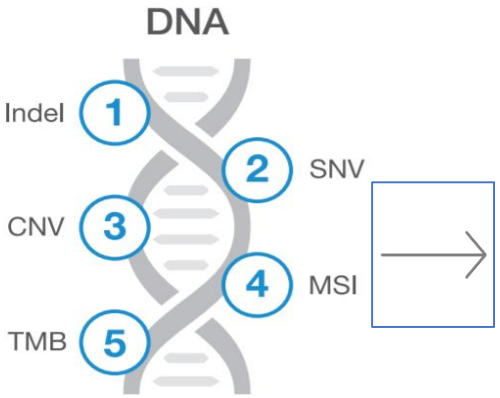


ABL1	BRD4	CUX1	FAM175A	GATA6	IGF1	MAP3K13	NOTCH4	POLE	RPTOR	TAF1
ABL2	BRIP1	CXCR4	FAM46C	GEN1	IGF1R	MAP3K14	NPM1	PPARG	RUNX1	TBX3
ACVR1	BTG1	CYLD	FANCA	GID4	IGF2	MAP3K4	NRAS	PPM1D	RUNX1T1	TCEB1
ACVR1B	BTK	DAXX	FANCC	GLI1	IKBKE	MAPK1	NRG1	PPP2R1A	RYBP	TCF3
AKT1	C11orf30	DCUN1D1	FANCD2	GNA11	IKZF1	MAPK3	NSD1	PPP2R2A	SDHA	TCF7L2
AKT2	CALR	DDR2	FANCE	GNA13	IL10	MAX	NTRK1	PPP6C	SDHAF2	TERC
AKT3	CARD11	DDX41	FANCF	GNAQ	IL7R	MCL1	NTRK2	PRDM1	SDHB	TERT
ALK	CASP8	DHX15	FANCG	GNAS	INHA	MDC1	NTRK3	PREX2	SDHC	TET1
ALOX12B	CBFB	DICER1	FANCI	GPR124	INHBA	MDM2	NUP93	PRKAR1A	SDHD	TET2
ANKRD11	CBL	DIS3	FANCL	GPS2	INPP4A	MDM4	NUTM1	PRKCI	SETBP1	TFE3
ANKRD26	CCND1	DNAJB1	FAS	GREM1	INPP4B	MED12	PAK1	PRKDC	SETD2	TFRC
APC	CCND2	DNMT1	FAT1	GRIN2A	INSR	MEF2B	PAK3	PRSS8	SF3B1	TGFBR1
AR	CCND3	DNMT3A	FBXW7	GRM3	IRF2	MEN1	PAK7	PTCH1	SH2B3	TGFBR2
ARAF	CCNE1	DNMT3B	FGF1	GSK3B	IRF4	MET	PALB2	PTEN	SH2D1A	TMEM127
ARFRP1	CD274	DOT1L	FGF10	H3F3A	IRS1	MGA	PARK2	PTPN11	SHQ1	TMPRSS2
ARID1A	CD276	E2F3	FGF14	H3F3B	IRS2	MITF	PARP1	PTPRD	SLIT2	TNFAIP3
ARID1B	CD74	EED	FGF19	H3F3C	JAK1	MLH1	PAX3	PTPRS	SLX4	TNFRSF14
ARID2	CD79A	EGFL7	FGF2	HGF	JAK2	MLL	PAX5	PTPRT	SMAD2	TOP1
ARID5B	CD79B	EGFR	FGF23	HIST1H1C	JAK3	MLLT3	PAX7	QKI	SMAD3	TOP2A
ASXL1	CDC73	EIF1AX	FGF3	HIST1H2BD	JUN	MPL	PAX8	RAB35	SMAD4	TP53
ASXL2	CDH1	EIF4A2	FGF4	HIST1H3A	KAT6A	MRE11A	PBRM1	RAC1	SMARCA4	TP63
ATM	CDK12	EIF4E	FGF5	HIST1H3B	KDM5A	MSH2	PDCD1	RAD21	SMARCB1	TRAF2
ATR	CDK4	EML4	FGF6	HIST1H3C	KDM5C	MSH3	PDCD1LG2	RAD50	SMARCD1	TRAF7
ATRX	CDK6	EP300	FGF7	HIST1H3D	KDM6A	MSH6	PDGFRA	RAD51	SMC1A	TSC1
AURKA	CDK8	EPCAM	FGF8	HIST1H3E	KDR	MST1	PDGFRB	RAD51B	SMC3	TSC2
AURKB	CDKN1A	EPHA3	FGF9	HIST1H3F	KEAP1	MST1R	PDK1	RAD51C	SMO	TSHR
AXIN1	CDKN1B	EPHA5	FGFR1	HIST1H3G	KEL	MTOR	PDPK1	RAD51D	SNCAIP	U2AF1
AXIN2	CDKN2A	EPHA7	FGFR2	HIST1H3H	KIF5B	MUTYH	PGR	RAD52	SOCS1	VEGFA
AXL	CDKN2B	EPHB1	FGFR3	HIST1H3I	KIT	MYB	PHF6	RAD54L	SOX10	VHL
B2M	CDKN2C	ERBB2	FGFR4	HIST1H3J	KLF4	MYC	PHOX2B	RAF1	SOX17	VTCN1
BAP1	CEBPA	ERBB3	FH	HIST2H3A	KLHL6	MYCL1	PIK3C2B	RANBP2	SOX2	WISP3
BARD1	CENPA	ERBB4	FLCN	HIST2H3C	KMT2B	MYCN	PIK3C2G	RARA	SOX9	WT1
BBC3	CHD2	ERCC1	FLI1	HIST2H3D	KMT2C	MYD88	PIK3C3	RASA1	SPEN	XIAP
BCL10	CHD4	ERCC2	FLT1	HIST3H3	KMT2D	MYOD1	PIK3CA	RB1	SPOP	XPO1
BCL2	CHEK1	ERCC3	FLT3	HLA-A	KRAS	NAB2	PIK3CB	RBM10	SPTA1	XRCC2
BCL2L1	CHEK2	ERCC4	FLT4	HLA-B	LAMP1	NBN	PIK3CD	RECQL4	SRC	YAP1
BCL2L11	CIC	ERCC5	FOXA1	HLA-C	LATS1	NCOA3	PIK3CG	REL	SRSF2	YES1
BCL2L2	CREBBP	ERG	FOXL2	HNF1A	LATS2	NCOR1	PIK3R1	RET	STAG1	ZBTB2
BCL6	CRKL	ERRFI1	FOXO1	HNRNPK	LMO1	NEGR1	PIK3R2	RFWD2	STAG2	ZBTB7A
BCOR	CRLF2	ESR1	FOXP1	HOXB13	LRP1B	NF1	PIK3R3	RHEB	STAT3	ZFHX3
BCORL1	CSF1R	ETS1	FRS2	HRAS	LYN	NF2	PIM1	RHOA	STAT4	ZNF217
BCR	CSF3R	ETV1	FUBP1	HSD3B1	LZTR1	NFE2L2	PLCG2	RICTOR	STAT5A	ZNF703
BIRC3	CSNK1A1	ETV4	FYN	HSP90AA1	MAGI2	NFKBIA	PLK2	RIT1	STAT5B	ZRSR2
BLM	CTCF	ETV5	GABRA6	ICOSLG	MALT1	NKX2-1	PMAIP1	RNF43	STK11	
BMPR1A	CTLA4	ETV6	GATA1	ID3	MAP2K1	NKX3-1	PMS1	ROS1	STK40	
BRAF	CTNNA1	EWSR1	GATA2	IDH1	MAP2K2	NOTCH1	PMS2	RPS6KA4	SUFU	
BRCA1	CTNNB1	EZH2	GATA3	IDH2	MAP2K4	NOTCH2	PNRC1	RPS6KB1	SUZ12	
BRCA2	CUL3	FAM123B	GATA4	IFNGR1	MAP3K1	NOTCH3	POLD1	RPS6KB2	SYK	

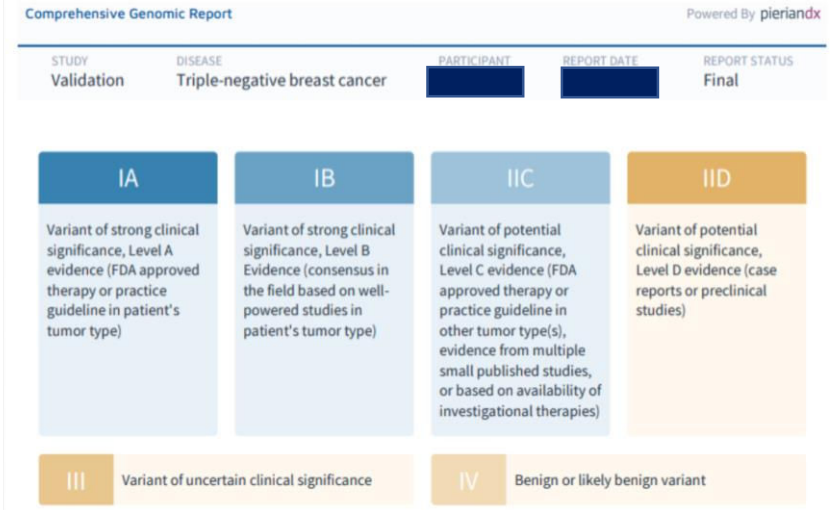
55

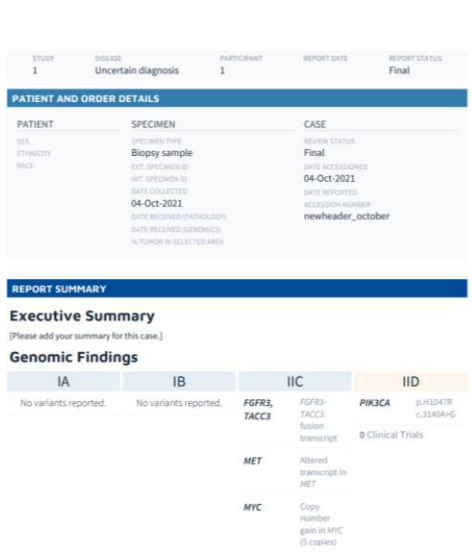
ABL1	BCL2	CSF1R	ESR1	EWSR1	FLI1	KIF5B	MSH2	NRG1	PAX7	RAF1
AKT3	BRAF	EGFR	ETS1	FGFR1	FLT1	KIT	MYC	NTRK1	PDGFRA	RET
ALK	BRCA1	EML4	ETV1	FGFR2	FLT3	MET	NOTCH1	NTRK2	PDGFRB	ROS1
AR	BRCA2	ERBB2	ETV4	FGFR3	JAK2	MLL	NOTCH2	NTRK3	PIK3CA	RPS6KB1
AXL	CDK4	ERG	ETV5	FGFR4	KDR	MLLT3	NOTCH3	PAX3	PPARG	TMPRSS2

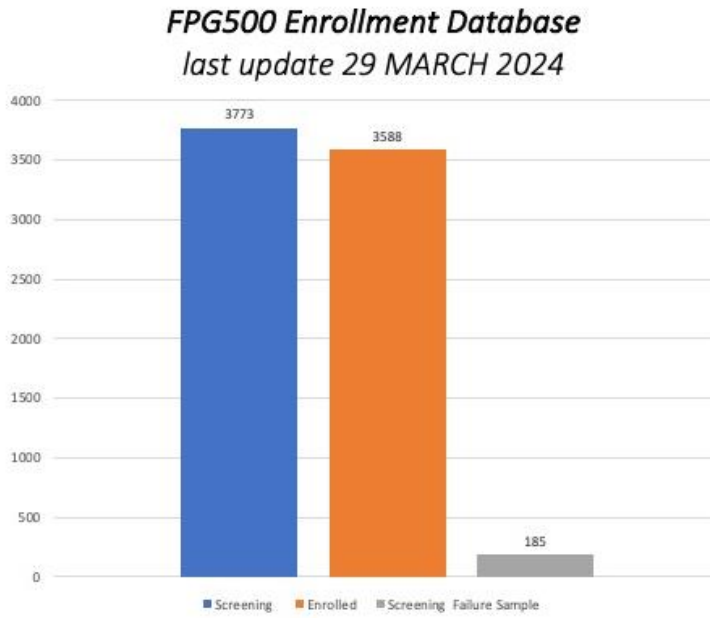
Report usato per il MTB del Policlinico Universitario Gemelli IRCCS

Il MTB istituzionale aiuta i clinici a interpretare e gestire report complessi di “genomic profiling”. In particolare il MTB discute tutti i casi con varianti documentate per cui non esiste un farmaco approvato, per verificare la disponibilità di trial clinici o usi off label di farmaci (i.e. expanded access program ecc.)

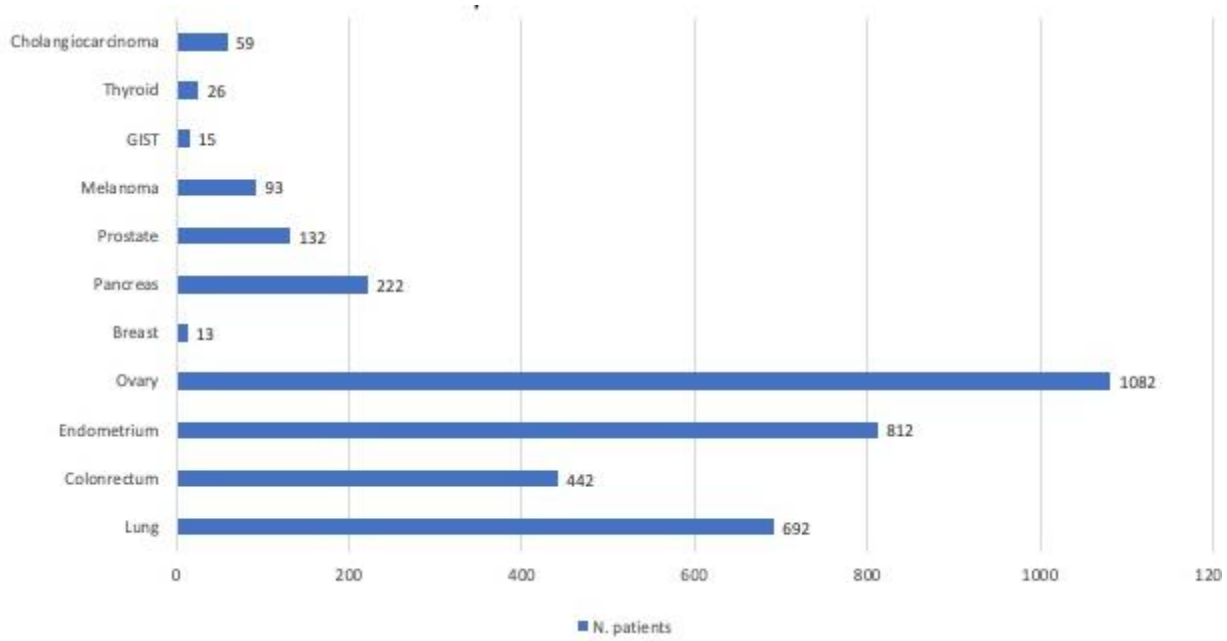
Genomic alterations are reported according to nomenclature of Human Genome Variation Society (HGVS) and classified according to Association for Medical Pathology (AMP), ASCO, and the College of American Pathologists classification system into **tiers IA, IB, IIC, IID, III and IV**, stratified according to clinical usefulness ('actionability')



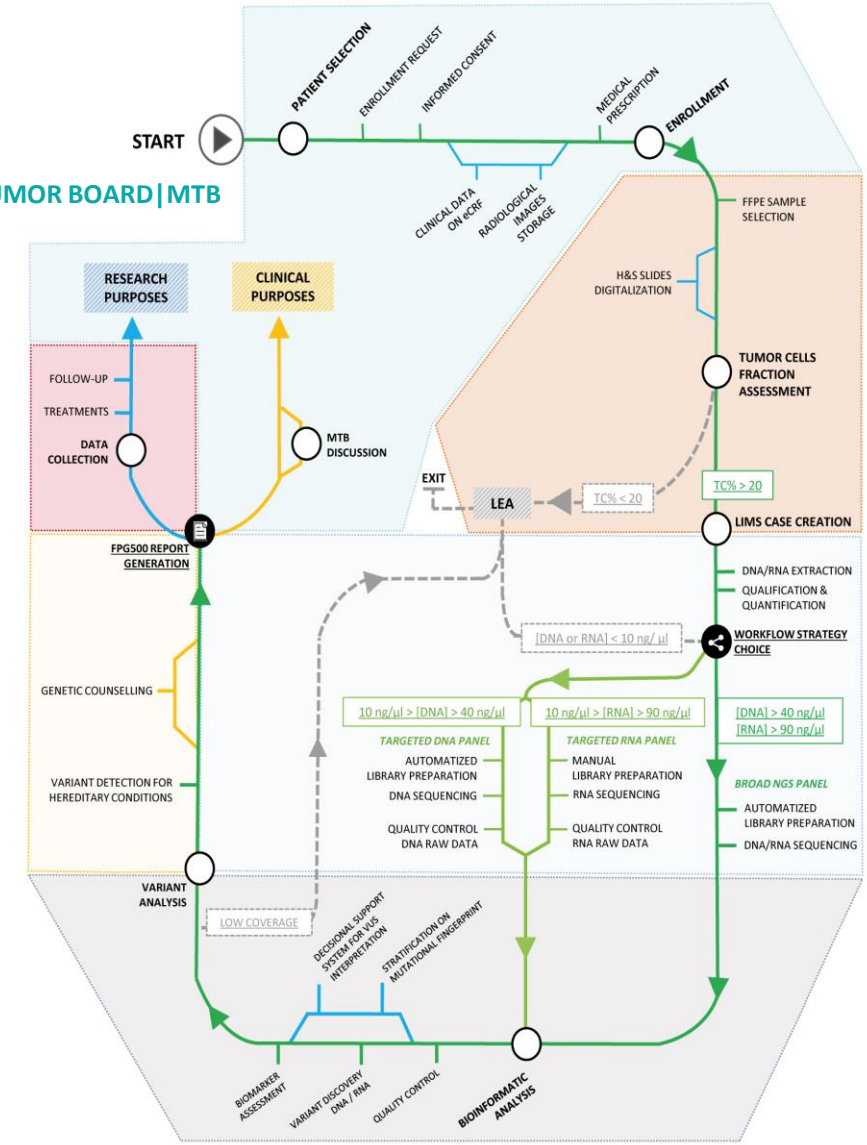




Profilazione genomica completa FPG500

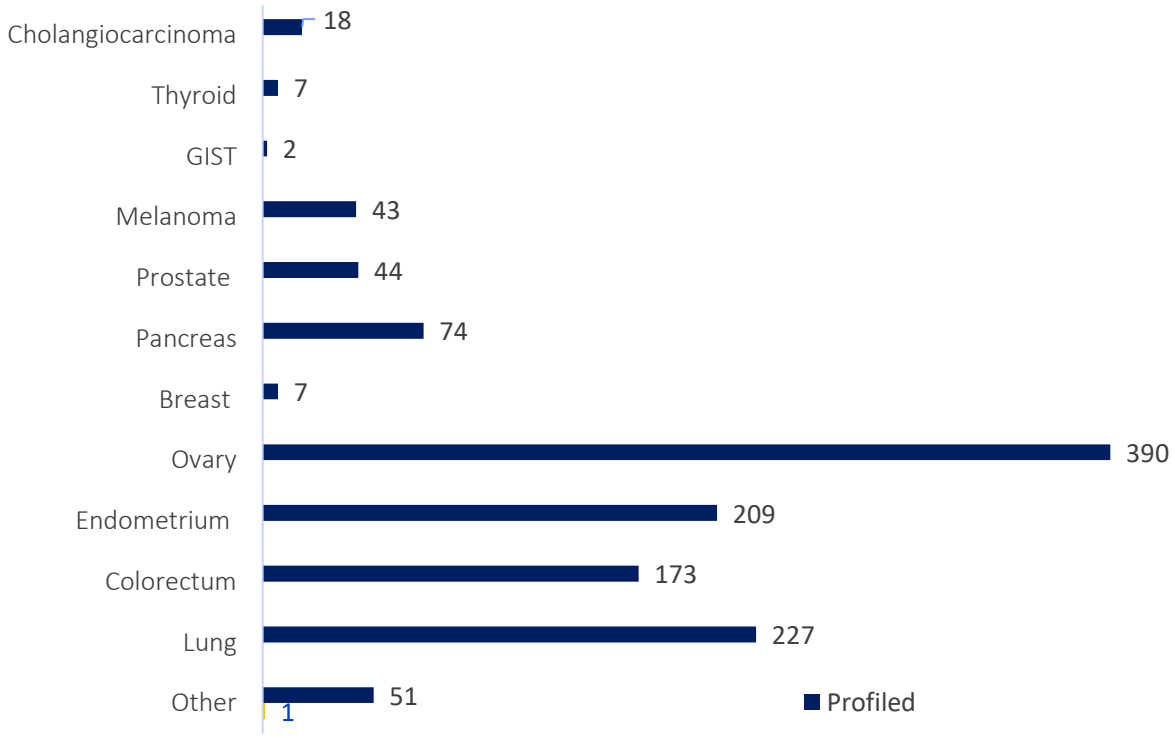


PATHWAY


START
PATIENT SELECTION
ENROLLMENT REQUEST
INFORMED CONSENT
CLINICAL DATA ON eCRF
RADIOLOGICAL IMAGES STORAGE
MEDICAL PRESCRIPTION
ENROLLMENT
CLINICIANS | TUMOR BOARD|MTB
RESEARCH PURPOSES
CLINICAL PURPOSES
FOLLOW-UP
TREATMENTS
DATA COLLECTION
MTB DISCUSSION
DATA COLLECTION CORE FACILITY
FFPE SAMPLE SELECTION
H&S SLIDES DIGITALIZATION
TUMOR CELLS FRACTION ASSESSMENT
PATHOLOGY UNIT
EXIT
LEA
TC% < 20
TC% > 20
LIMS CASE CREATION
FPG500 REPORT GENERATION
DNA/RNA EXTRACTION
QUALIFICATION & QUANTIFICATION
[DNA or RNA] < 10 ng/ µl
WORKFLOW STRATEGY CHOICE
GENETIC COUNSELLING
MEDICAL GENETICS UNIT
10 ng/µl > [DNA] > 40 ng/µl
10 ng/µl > [RNA] > 90 ng/µl
[DNA] > 40 ng/µl [RNA] > 90 ng/µl
TARGETED DNA PANEL
AUTOMATIZED LIBRARY PREPARATION
DNA SEQUENCING
TARGETED RNA PANEL
MANUAL LIBRARY PREPARATION
RNA SEQUENCING
BROAD NGS PANEL
AUTOMATIZED LIBRARY PREPARATION
DNA/RNA SEQUENCING
VARIANT DETECTION FOR HEREDITARY CONDITIONS
QUALITY CONTROL DNA RAW DATA
QUALITY CONTROL RNA RAW DATA
GENOMICS CORE FACILITY
VARIANT ANALYSIS
LOW COVERAGE
DECISIONAL SUPPORT SYSTEM FOR VUS INTERPRETATION
STRATIFICATION ON MUTATIONAL FINGERPRINT
BIOMARKER ASSESSMENT
VARIANT DISCOVERY DNA / RNA
QUALITY CONTROL
BIOINFORMATIC ANALYSIS
BIOINFORMATICS CORE FACILITY

RESULTS

Comprehensive cancer genome profiling programme FPG500 | 1 Jan 2022- 19 Nov 2022



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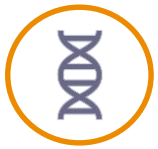
Critical unmet needs to be addressed



- A global harmonization in cancer sequencing practices and procedures
- No MTB without implementation of Comprehensive Cancer Genome Profiling (CGP)

- MTBs need a standardization of **operational requirements** and an appropriate unsolicited findings **policy**

- It is important to keep such programmes in an **academic context**
- Data from MTBs are crucial also for **policy makers** regarding drugs access and **companies** providing interpretation services for CGP

Gemelli Comprehensive Cancer Center

Integrazione del Comprehensive Cancer Center con il Clinical Trial Center e il progetto Big Data *Generator*