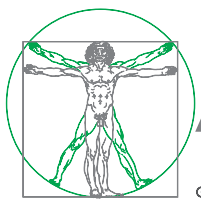
Guida alla consultazione del report TruSight Oncology500 (TSO500)



AMES Group

GENETICA MEDICA · MICROBIOLOGIA · PATOLOGIA CLINICA

Di seguito il report **PierianDX**, questo documento riporta il risultato delle analisi per il kit **TSO500**, nella prima pagina (vedi sotto) è presente il riassunto di tutte le informazioni.
Vediamole in dettaglio:

TruSight™ Oncology 500
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PierianDx
77 Maryland Plaza
St. Louis, MO 63108
CLIENT LOGO

PATIENT	DISEASE	MEDICAL RECORD #	REPORT DATE	REPORT STATUS
John Doe	Non-small cell Lung Cancer	6563465346	02/18/2019	Final

Report Summary

GENOMIC FINDINGS BY TIER + LEVEL: 2 (IA) | 0 (IB) | 1 (IIC) | 0 (IID)
TMB: 24 muts/Mb — high (status)
MSI: 5% Unstable Sites — stable (status)
CLINICAL TRIALS: 13

SPECIMEN & ORDER

PATIENT

DATE OF BIRTH	02/04/1981
SEX	Male
ETHNICITY	Not Hispanic or Latino
RACE	White

PHYSICIAN

ORDERING PHYSICIAN	Bruce Banner
FACILITY	Organization Name

SPECIMEN

SPECIMEN TYPE	Specimen from lung
EXT. SPECIMEN ID	48998243
DATE COLLECTED	02/05/2019 13:53
DATE RECEIVED	02/08/2019 12:44
% TUMOR IN SELECTED AREA	25

CASE

REVIEW STATUS	Final
DATE ACCESSIONED	02/15/2019
DATE REPORTED	Not Available
ACCESSION #	ILMN_447

GENOMIC FINDINGS

Tier I - Strong Clinical Significance

VARIANT	LEVEL	VAF %	CLINICAL IMPACT
NCOA4-RET fusion	A	-	**Responsive To** - Cabozantinib, Vandatinib *in non-small cell lung cancer*
KRAS p.G12D c.35G>A	A	10.0	**Non-Responsive To** - Erlotinib, Gefitinib, Afatinib, Osimertinib, Dacomitinib **Unfavorable Prognosis In** - non-small cell lung cancer

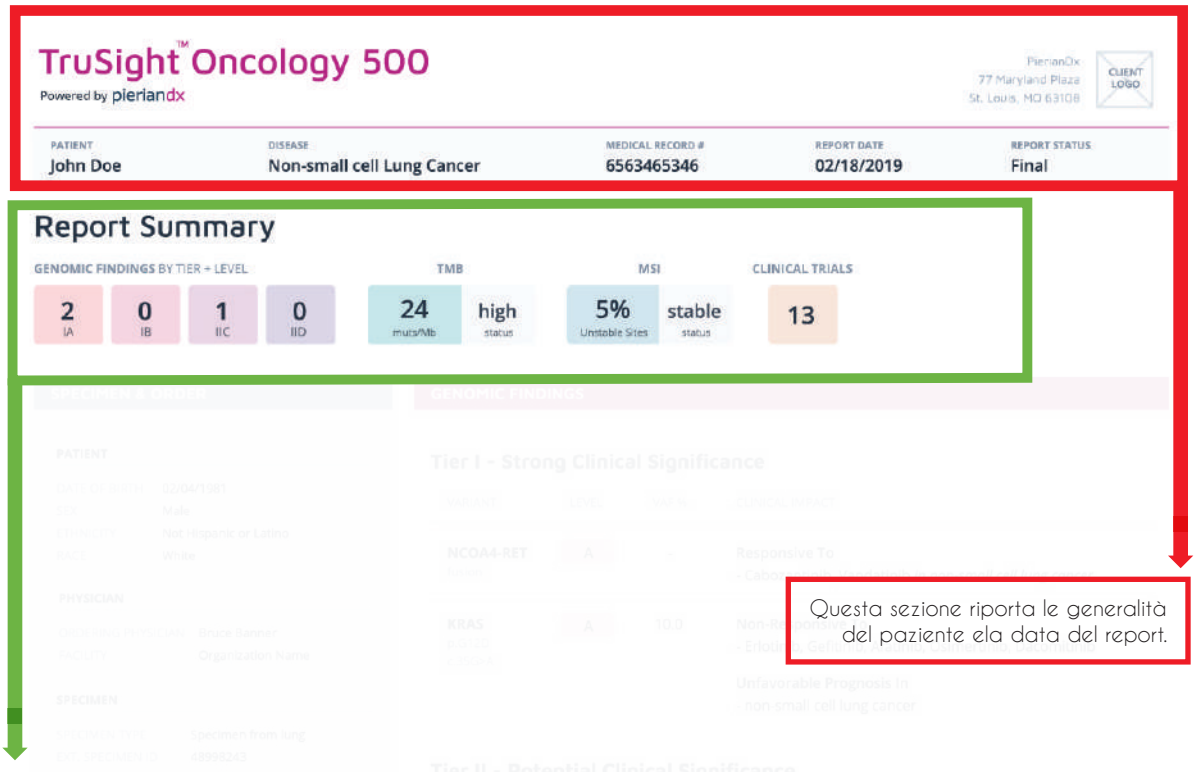
Tier II - Potential Clinical Significance

VARIANT	LEVEL	VAF %	CLINICAL IMPACT
PDGFRA p.D842V c.2525A>T	C	15.0	**Responsive To** - Dasatinib *in gastrointestinal stromal tumor* **Non-Responsive To** - Sunitinib, Imatinib *in gastrointestinal stromal tumor*

Other Biomarkers

BIOMARKER	STATUS	VALUE	CLINICAL IMPACT
TMB	High	24 muts/Mb	**Responsive To** - Nivolumab, Nivolumab + Ipilimumab *in non-small cell lung cancer*
MSI	Stable	5% Unstable Sites	

Sotto è riportata la prima parte del documento che costituisce la parte riassuntiva.



Questa sezione riporta le generalità del paziente ela data del report.

Questa sezione riporta riassunte e raggruppate tutte le informazioni che emergono dal report.

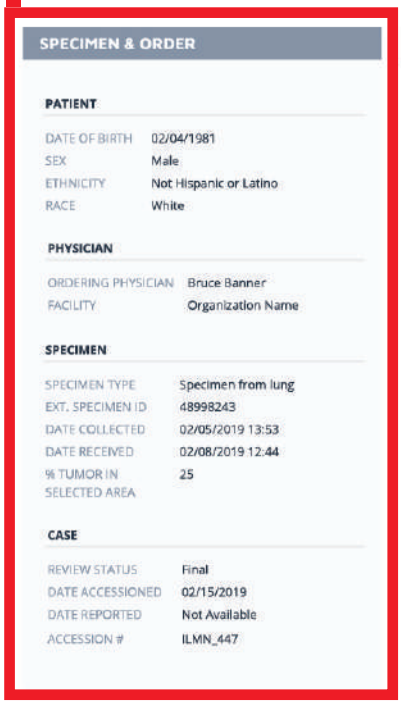
A sinistra troviamo le mutazioni presenti nel paziente divise in 4 gruppi che sono:

- Tier I varianti dal forte significato clinico
- Tier II varianti dal potenziale significato clinico
- Tier III varianti dal significato clinico sconosciuto
- Tier IV varianti benigne

Di fianco sono riportati i valori per il Tumor Mutationnal Burden (**TMB**), un valore che indica quanto il paziente sia idoneo per le innovative cure immunologiche.
Ancora a destra è presnete l'instabilità microsatellitare (**MSI**) anch'esso un importante fattore prognostico.
L'ultimo valore della riga a destra, indica i Clinical Trials più pertinenti a livello mondiale per il tipo di patologia.

Il dettaglio della prima parte del report.

Questa sezione riporta informazioni più dettagliate rispetto al paziente e alla struttura sanitaria che l'ha preso in carico, nonchè al tipo di campione biologico utilizzato.



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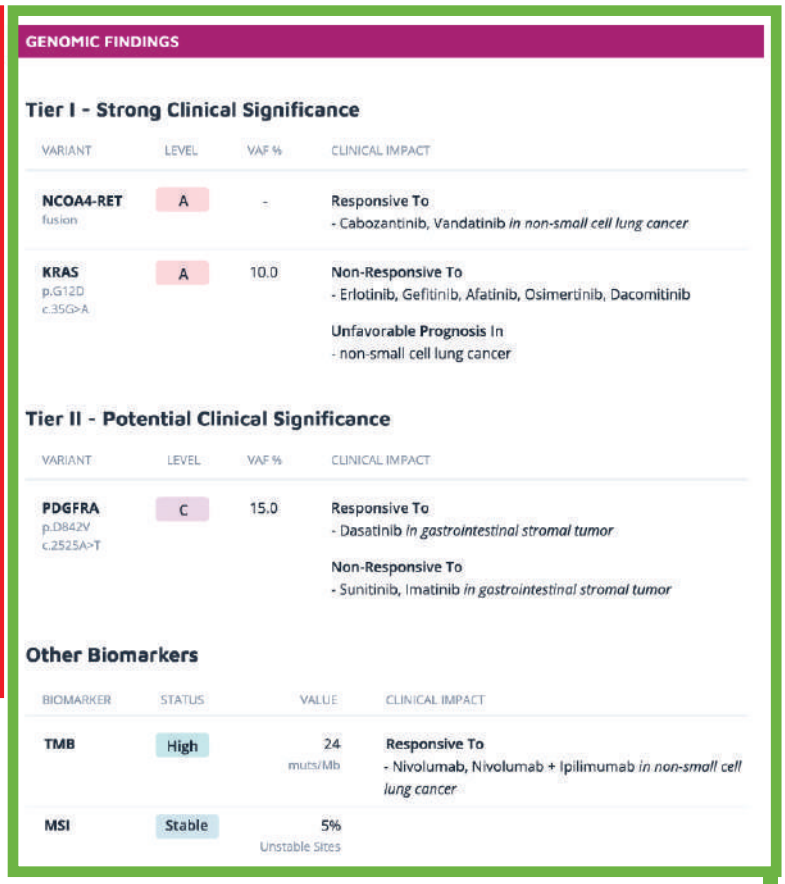

GENOMIC FINDINGS

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In questa sezione sono riportati maggiori dettagli riguardo le mutazioni trovate come ad esempio il gene in cui la mutazione è presnete, la frequenza allelica e la responsività ai vari farmaci. Inoltre ci sono anche i dettagli riguardanti i già citati marcatori prognostici **TMB** ed **MSI**.

In questa pagina si approfondisce il dettaglio delle mutazioni trovate, spiegando in maniera estensiva la funzione del gene e della mutazione stessa e le terapie al momento disponibili.

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PATIENT	DISEASE	MEDICAL RECORD #	REPORT DATE	REPORT STATUS
John Doe	Non-small cell Lung Cancer	6563465346	02/18/2019	Final

CLINICALLY RELEVANT RESULTS

Tier I - Strong Clinical Significance

VARIANT	INTERPRETATION
NCOA4-RET fusion A	RET encodes a receptor tyrosine kinase involved in cell growth and differentiation which is known to undergo oncogenic activation in vivo and in vitro by cytogenetic rearrangement (provided by RefSeq, Jul 2008). NCOA4 encodes an androgen receptor coactivator which interacts with the androgen receptor in a ligand-dependent manner to enhance its transcriptional activity. Chromosomal translocations between NCOA4 and RET, both located on chromosome 10, have been associated with papillary thyroid carcinoma (provided by RefSeq, Feb 2009). RET rearrangements resulting in fusion with partner genes including KIF5B, CCDC6 and NCOA4 have been reported in non-small cell lung cancer (NSCLC) patients(PMID- 29128428). A NCOA4-RET fusion is identified in this case. The N terminus of the NCOA4 gene fuses with the C terminus of the RET gene in this fusion (PMID- 28011461). In PCCL3 cells, expression of NCOA4-RET fusion was reported to simultaneously activate DNA synthesis and apoptosis apart from interfering with thyroid differentiation at steps distal to the TSH-R (PMID- 12690093, 2003). The NCOA4-RET fusion has been reported in patients with NSCLC specifically in lung adenocarcinoma patients (COSMIC, February 2019, PMID- 23150706). RET rearrangements are one of the emerging biomarkers to identify novel therapies for patients with metastatic NSCLC (NCCN, NSCLC v.3.2019). NCCN recommends cabozantinib and vandatinib (category 2A) as targeted agents for NSCLC patients harbouring RET rearrangements (NCCN, NSCLC v.3.2019).
KRAS p.G12D c.35G>A A NM_004985.3 VAF % 10.0 DEPTH 5663	The KRAS protein has intrinsic GTPase activity and is an important mediator of growth factor receptor signaling resulting in the activation of several downstream pathways such as PI3K-mTOR and RAS-RAF-MEK pathway (RefSeq, Jul 2008). A missense alteration in KRAS, G12D, is identified in this case. Codon 12 lies within a GTP binding region of the KRAS protein (UniProt.org). Mutations in KRAS at codon 12 (within the GTP binding region), including KRAS G12D, result in reduced GTPase activity, which in turn leads to constitutive activation of KRAS and its downstream PI3K-AKT and MAPK signaling pathways (PMID- 26902995; 25705018). In ClinVar, KRAS G12D has been classified as 'Pathogenic' in several malignancies ('Pathogenic' for somatic in malignancies including non-small cell lung cancer) (Variation ID: 12582). KRAS G12D is reported in malignancies including non-small cell lung cancer (COSMIC, February 2019). Approximately 25% of patients with lung adenocarcinomas in a North American population have KRAS mutations (NCCN, NSCLC v3.2019). KRAS mutation prevalence has been associated with cigarette smoking (NCCN, NSCLC v3.2019). In NSCLC, the presence of a KRAS mutation is prognostic of poor survival when compared to patients with tumors without KRAS mutation, independent of therapy (NCCN, NSCLC v3.2019). KRAS mutations have a predictive role in brain metastases incidence, recurrence and outcome in Caucasian NSCLC patients (PMID- 27999344; 26616848). Mutations in KRAS have been associated with reduced responsiveness to EGFR TKI therapy and do not appear to affect chemotherapeutic efficacy (NCCN, NSCLC v3.2019). Targeted therapy is currently not available for patients with KRAS mutations, although immune checkpoint inhibitors appear to be effective; MEK inhibitors are in clinical trials (NCCN, NSCLC v3.2019).

Tier II - Potential Clinical Significance

VARIANT	INTERPRETATION
PDGFRA p.D842V c.2525A>T C NM_006206.4 VAF % 15.0 DEPTH 7986	PDGFR-alpha (PDGFRA) is a receptor protein kinase that activates the PI3K/AKT/mTOR and MAPK/ERK pathways and promotes activation of STAT family members STAT1, STAT3 and STAT5A and/or STAT5B (UniProt.org). A missense alteration in PDGFRA, D842V, is identified in this case. Codon 842 lies in exon 18, within the protein kinase domain of PDGFRA (UniProt.org). PDGFRA D842V is reported to be an activating, in vitro (PMID- 27349873; 12949711, 2003). In ClinVar, somatic PDGFRA D842V is reported as 'Pathogenic' in gastrointestinal stromal tumor (GIST) (Variation ID: 13543). PDGFRA D842V has been reported in Non-small cell lung cancer (COSMIC, February 2019). About 5% to 10% of GISTs have a mutation in the gene encoding PDGFRA receptor tyrosine kinase and PDGFRA exon 18 mutations are common in gastric GISTs (NCCN, Soft Tissue Sarcoma, v1.2019). Identification of activating kinase mutations in PDGFRA is an ancillary technique useful in the diagnosis of sporadic and familial GIST (NCCN, Soft Tissue Sarcoma, v1.2019). PDGFRA exon 18 mutations (including D842V) are associated with a better prognosis in GIST patients (NCCN, Soft Tissue Sarcoma, v1.2019). Primary imatinib resistance is commonly seen in GIST patients with mutations including PDGFRA D842V (NCCN, Soft Tissue Sarcoma,v1.2019; PMID- 30506540). A small number of GIST patients with a primary or secondary D842V mutation did not respond to sunitinib treatment (NCCN Soft Tissue Sarcoma v1.2019; PMID- 30224936). Dasatinib has demonstrated activity against PDGFRA D842V mutation, and it could be an effective treatment option for imatinib-resistant GIST patients (NCCN, Soft Tissue Sarcoma v1.2019).

Nella pagina che segue la parte superiore (riquadro verde) spiega il significato dei due biomarkers **TMB** ed MSI che sono una parte importante di questa analisi in termini di individuazione di una cura adeguata. Nella parte inferiore (riquadro rosso) sono elencati tutti i trial clinici e la loro relativa fase di sperimentazione per le varianti trovate.

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PATIENT	DISEASE	MEDICAL RECORD #	REPORT DATE	REPORT STATUS
John Doe	Non-small cell Lung Cancer	6563465346	02/18/2019	Final

Other Biomarkers

BIOMARKER	INTERPRETATION
TMB High 24 muts/Mb	Tumor mutational burden is an emerging quantitative genomic biomarker used to predict sensitivity to checkpoint inhibitors. NCCN recommends nivolumab with or without ipilimumab for patients with high TMB based on a recent study and the results of a Phase III clinical trial, NCT02477826 (NSCLC v3.2019, PMID: 29658845, 28636851)
MSI Stable 5% Unstable Sites	Microsatellite Instability is caused by a failure of the DNA mismatch repair system (MMR) and a predictor of favorable response to immunotherapies (PMID: 26028255). This patient does not exhibit evidence of High Microsatellite Instability (MSI).

CLINICAL TRIALS

TITLE	TRIAL IDENTIFIER	PHASE	VARIANT
Randomized Phase III Trial of Local Consolidation Therapy (LCT) After Nivolumab and Ipilimumab for Immunotherapy- Naive Patients With Metastatic Non-Small Cell Lung Cancer (LONESTAR) - Strategic Alliance: BMS	**NCT03391869** https://clinicaltrials.gov/show/NCT03391869	III	**NCOA4-RET** fusion
A Phase II Study of Cabozantinib in Patients With RET Fusion- Positive Advanced Non- Small Cell Lung Cancer and Those With Other Genotypes: ROS1 or NTRK Fusions or Increased MET or AXL Activity	**NCT01639508** https://clinicaltrials.gov/show/NCT01639508	II	**NCOA4-RET** fusion
Study of Regorafenib in Combination With Oral Methotrexate for KRAS Mutated Non-Small Cell Lung Cancer (NSCLC)	**NCT03520842** https://clinicaltrials.gov/show/NCT03520842	II	**KRAS** p.G12D c.35G>A
Molecular Profiling and Targeted Therapy for Advanced Non-Small Cell Lung Cancer, Small Cell Lung Cancer, and Thymic Malignancies	**NCT01306045** https://clinicaltrials.gov/show/NCT01306045	II	**PDGFRA** p.D842V c.2525A>T
A Pilot Study of Pazopanib in Molecularly Selected Patients With Advanced Non- Small Cell Lung Cancer (NSCLC)	**NCT02193152** https://clinicaltrials.gov/show/NCT02193152	I	**NCOA4-RET** fusion
A Pilot Study of Nintedanib in Molecularly Selected Patients With Advanced Non- Small Cell Lung Cancer (NSCLC)	**NCT02299141** https://clinicaltrials.gov/show/NCT02299141	I	**NCOA4-RET** fusion
A Phase 1/1b Study of MGCD516 in Patients With Advanced Solid Tumor Malignancies	**NCT02219711** https://clinicaltrials.gov/show/NCT02219711	I	**NCOA4-RET** fusion
A Phase 1b Study of Abemaciclib in Combination With Pembrolizumab for Patients With Stage IV Non- Small Cell Lung Cancer or Hormone Receptor Positive, HER2 Negative Breast Cancer	**NCT02779751** https://clinicaltrials.gov/show/NCT02779751	I	**KRAS** p.G12D c.35G>A
A Phase Ib, Open-label, Multicenter Study of Oral LXH254 in Combination With Oral LTT462 in Adult Patients With Advanced or Metastatic KRAS or BRAF Mutant Non- Small Cell Lung Cancer	**NCT02974725** https://clinicaltrials.gov/show/NCT02974725	I	**KRAS** p.G12D c.35G>A

Nella parte inferiore della pagina, in ogni riquadro grigio c'è una variante dal significato clinico sconosciuto con l'indicazione del gene, l'alterazione amminoacidica e nucleotidica.

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A Phase I Dose Finding Study of Oral LXH254 in Adult Patients With Advanced Solid Tumors Harboring MAPK Pathway Alterations — NCT02607813 — KRAS

A Phase Ib Trial of Pembrolizumab (MK-3475) and Trametinib Focused on Advanced KRAS Mutant Non-small Cell Lung Cancer — NCT03299088 — KRAS

Phase 1/1b Study of MGCD516 in Patients With Advanced Cancer — NCT02219711 — PDGFRA

Nintedanib in Molecularly Selected Patients With Advanced Non-Small Cell Lung Cancer — NCT02299141 — PDGFRA

TIER III - VARIANTS OF UNKNOWN SIGNIFICANCE

AKT3 p.P449S NM_001206729.1 c.1345C>T	AKT3 p.E450K NM_001206729.1 c.1348G>A	APC p.V2194I NM_000038.5 c.6580G>A	APC p.D1794V NM_000038.5 c.5381A>T	APC p.A1793E NM_000038.5 c.5378C>A	APC p.N1792K NM_000038.5 c.5376T>A	APC p.L148H NM_000038.5 c.443T>A	APC p.L148I NM_000038.5 c.442C>A
ATM p.N1240Kfs*4 NM_000051.3 c.3720_3736del17	ATM p.G301Vfs*19 NM_000051.3 c.900delA	BRCA2 p.S2984* NM_000059.3 c.8951C>A	BRCA2 p.S2984T NM_000059.3 c.8950T>A	BRCA2 p.E2301K NM_000059.3 c.6901G>A	BRCA2 p.I2296M NM_000059.3 c.6888A>G	BRCA2 p.D2294E NM_000059.3 c.6882C>G	BRCA2 p.N2291D NM_000059.3 c.6871A>G
BRCA2 p.P2283H NM_000059.3 c.6848C>A	BRCA2 p.P2283T NM_000059.3 c.6847C>A	BRCA2 p.G1761E NM_000059.3 c.5282G>A	BRCA2 p.D1737V NM_000059.3 c.5210A>T	BRCA2 p.D1737Y NM_000059.3 c.5209G>T	BRCA2 p.E1734* NM_000059.3 c.5200G>T	BRCA2 p.E1734K NM_000059.3 c.5200G>A	BRCA2 p.L1732P NM_000059.3 c.5195T>C
BRCA2 p.H1731N NM_000059.3 c.5191C>A	BRCA2 p.Y1313* NM_000059.3 c.3939C>A	BRCA2 p.Y1313C NM_000059.3 c.3938A>G	BRCA2 p.T1310I NM_000059.3 c.3929C>T	BRCA2 p.T1310Mfs*25 NM_000059.3 c.3929delC	BRCA2 p.N1297K NM_000059.3 c.3891T>A	BRCA2 p.N1287Ifs*6 NM_000059.3 c.3860delA	BRCA2 p.S1284R NM_000059.3 c.3852T>G
BRCA2 p.S1284R NM_000059.3 c.3852T>A	BRCA2 p.V1283I NM_000059.3 c.3847G>A	BRCA2 p.V1283* NM_000059.3 c.3847delG	BRCA2 p.E866K NM_000059.3 c.2596G>A	BRCA2 p.P606Q NM_000059.3 c.1817C>A	BRCA2 p.Q347K NM_000059.3 c.1039C>A	CCND3 p.S178A NM_001136017.2 c.532T>G	CTNNB1 p.N287S NM_001098209.1 c.860A>G
KRAS p.R164Q NM_004985.3 c.491G>A	KRAS p.G174S NM_004985.3 c.520G>A	KRAS p.M188L NM_004985.3 c.562A>C	MSH2 p.N566K NM_000251.2 c.1698T>A	MSH2 p.T564N NM_000251.2 c.1691C>A	MSH2 p.Y563S NM_000251.2 c.1688A>C	MSH2 p.Y563N NM_000251.2 c.1687T>A	MSH2 p.E562D NM_000251.2 c.1686G>C
MSH2 p.E562V NM_000251.2 c.1685A>T	MSH2 p.E562* NM_000251.2 c.1684G>T	MSH2 p.E562Q NM_000251.2 c.1684G>C	MSH2 p.E561* NM_000251.2 c.1681G>T	MSH2 p.E561K NM_000251.2 c.1681G>A	MSH2 p.N560I NM_000251.2 c.1679A>T	MSH2 p.S558F NM_000251.2 c.1673C>T	MSH2 p.S558Y NM_000251.2 c.1673C>A
PIK3R1 p.Q92K NM_001242466.1 c.274C>A	RB1 p.S302Y NM_000321.2 c.905C>A	RB1 p.W195C NM_00321.2 c.58G>T					

In quest'ultima pagina troviamo la legenda che spiega il raggruppamento delle varianti, un piccolo riassunto della metologia e la dichiarazione di responsabilità.

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CLASSIFICATION AND LEVELS OF EVIDENCE

The variant classification system used in this report is based on joint consensus recommendations of the Association for Molecular Pathology, American Society of Clinical Oncology, and the College of American Pathologists (J Mol Diagn 2017, 19:4-23). Tiers IA, IB, IIC, IID, III and IV describe variant categories of descending clinical significance in the patient. Variants in Tier IV are not reported in accordance with the consensus recommendations.

IA	IB	IIC	IID
Variant of strong clinical significance, Level A evidence (FDA approved therapy or practice guideline in patient's tumor type)	Variant of strong clinical significance, Level B Evidence (consensus in the field based on well-powered studies in patient's tumor type)	Variant of potential clinical significance, Level C evidence (FDA approved therapy or practice guideline in other tumor type(s), evidence from multiple small published studies, or based on availability of investigational therapies)	Variant of potential clinical significance, Level D evidence (case reports or preclinical studies)

III	Variant of unknown clinical significance
IV	Benign or likely benign variant

METHODOLOGY

Experimental Methodology: This test uses targeted next-generation sequencing to analyze coding regions of the most inclusive annotated RefSeq transcript for each of the targeted genes. Target enrichment was performed using TruSight Oncology 500 workflow (Illumina). Sequencing of enriched libraries was performed in multiplex on the Illumina NextSeq using the paired-end, 150 base-pair configuration.

Informatics Methodology: Secondary analysis was performed using Illumina's TruSight Oncology 500 Local App version 1.3.1.

DISCLAIMER

This Report was generated using the materials and methods described below, which required the use of various reagents, protocols, instruments, software, databases, and other items, some of which were provided or made accessible by third parties. A defect or malfunction in any such reagents, protocols, instruments, software, databases, and/or other items may compromise the quality or accuracy of the Report.

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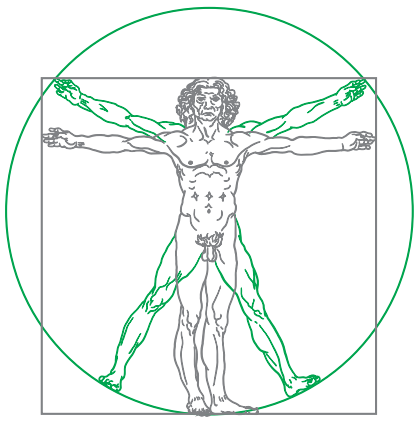

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