THE ROLE OF COMPREHENSIVE GENOMIC PROFILING IN EMERGING BIOMARKER TESTING

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FONDAZIONE "G. Pascale" – NAPOLI

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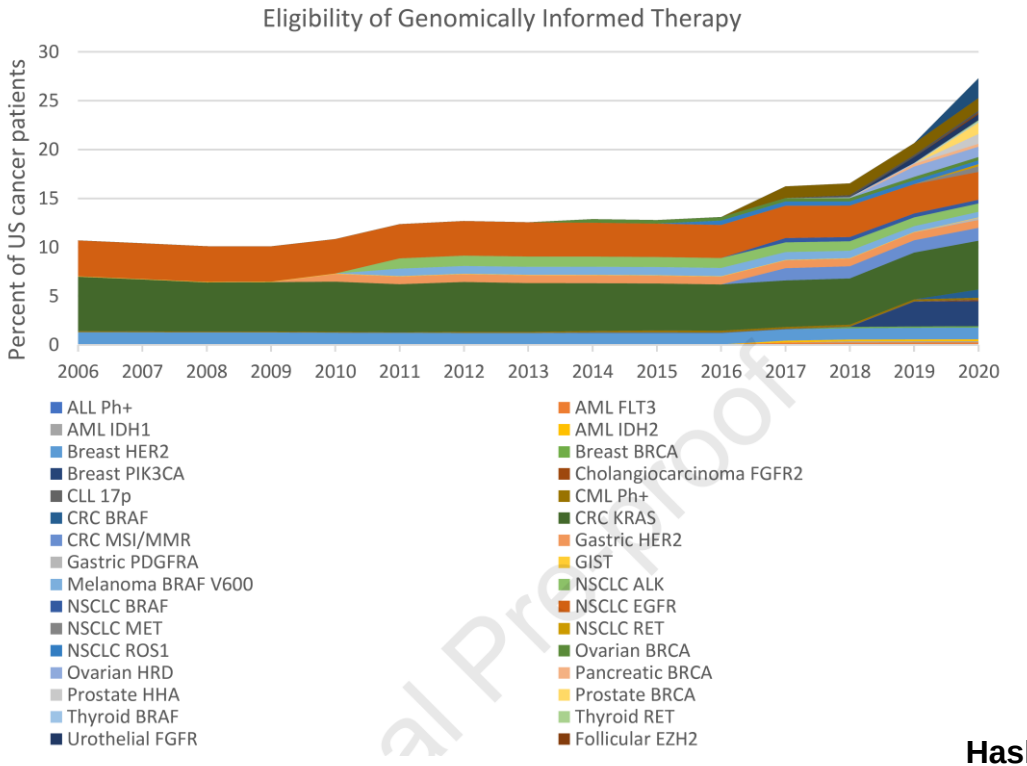
- **Non-financial interests:** President, International Quality Network for Pathology (IQN Path); President, Italian Cancer Society (SIC)

AGENDA

- Precision Oncology – current landscape
- TMB testing in clinical research
- cfDNA Analysis in clinical research
- Current status of biomarker testing in Europe

PRECISION ONCOLOGY – CURRENT LANDSCAPE

Estimated eligibility of genome informed therapy in US cancer patients, 2006-2020



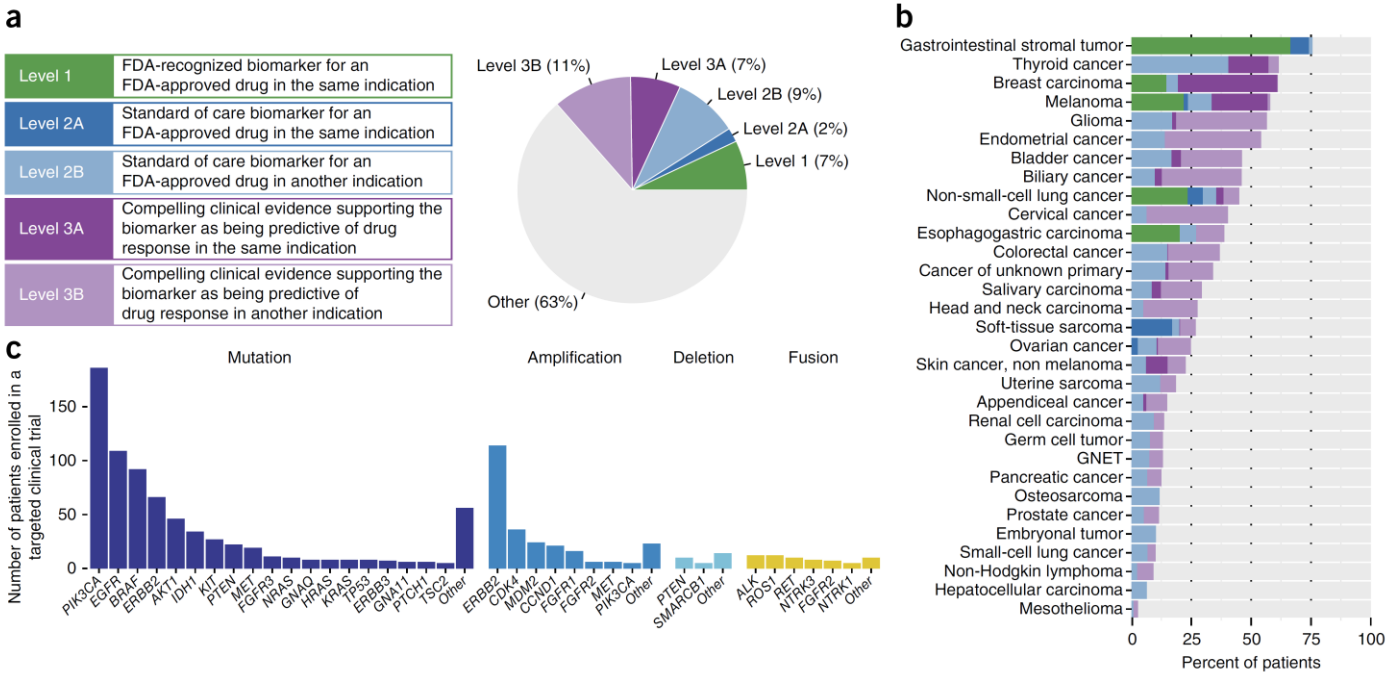
Haslam Ann Oncol 2021

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 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 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 tumour NGS can be an alternative option to PCR if it does not create 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. In this latter case, 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).		

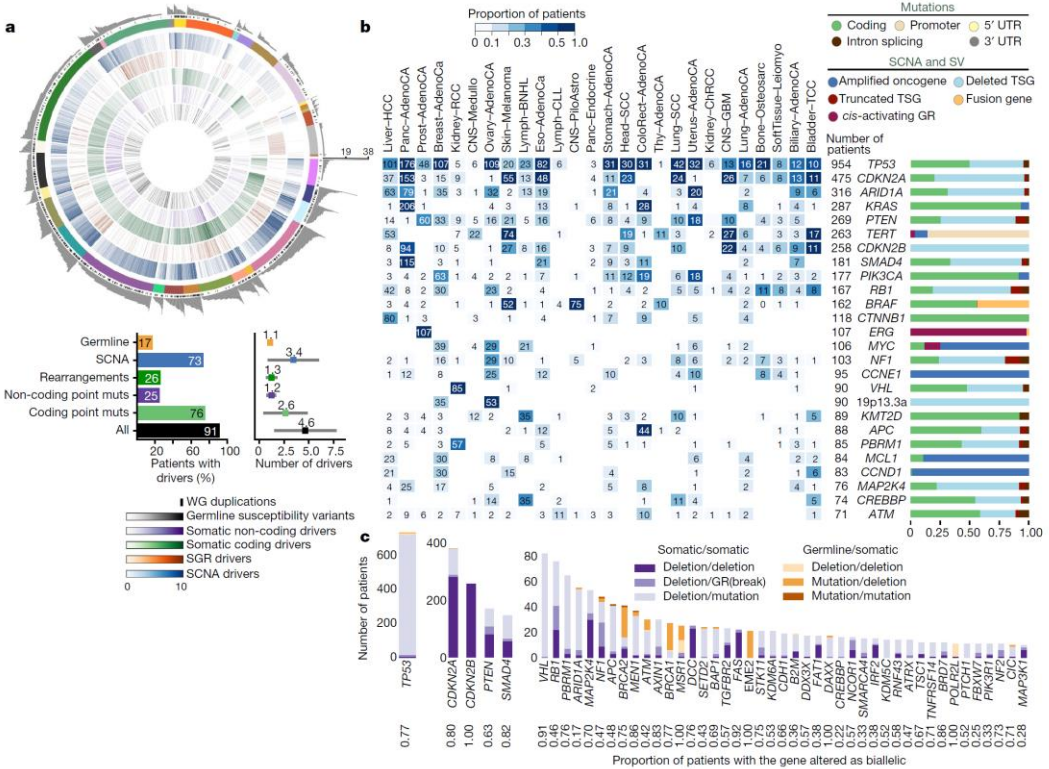
Mosele Ann Oncol 2020

NGS detectable mutations



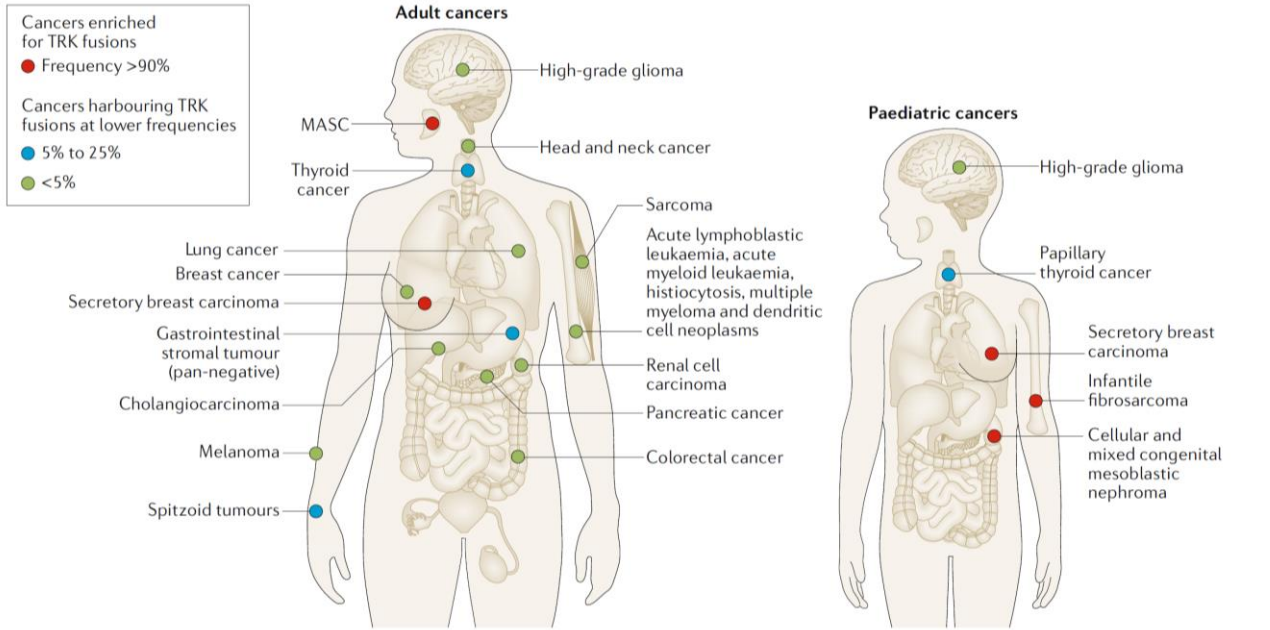
Zehir Nat Med 2017

Driver mutations in PCAWG: the search of tumor agnostic biomarkers



The ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium NATURE 2020

Distribution and frequency of NTRK fusions in adult and paediatric tumours



Cocco Nat Rev Clin Oncol 2018

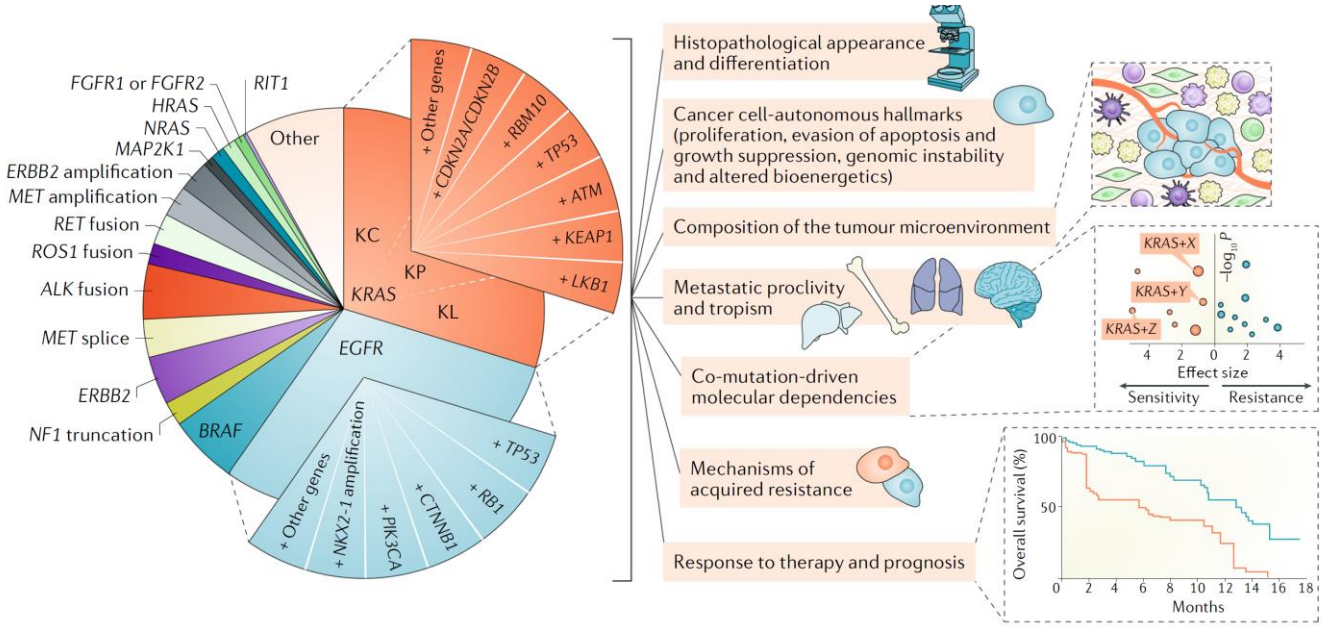
Molecular alterations with potential for future histology-agnostic designation

Molecular alteration	Therapeutic agent	Trial characteristics[a]	Study population	Preliminary efficacy results
RET fusions	Selpercatinib[130]	Phase I/II trial (LIBRETTO-001)	$n = 531$; NSCLC ($n = 253$); MTC ($n = 226$); PTC ($n = 27$); other ($n = 25$)	ORR: 66% for NSCLC, 51% for MTC, 62% for PTC; CRs: 2% for NSCLC, 6% for MTC, 0% for PTC; DCR: 98% for NSCLC, 95% for MTC, 100% for PTC; mDOR: 20 months for NSCLC, NR for MTC and PTC; mPFS: NR
	Pralsetinib[147]	Phase I/II trial (ARROW)	$n = 144$; three tumour types: NSCLC ($n = 79$); MTC ($n = 60$); PTC ($n = 5$)	ORR: 58% for NSCLC, 46% for MTC, 50% for PTC; CRs: 1% for NSCLC, 1% for MTC, 0% for PTC; DCR: 96% for NSCLC, 97% for MTC, 100% for PTC; mDOR: NR; mPFS: NR
	RXDX-105 (REF.[148])	Phase I/Ib trial	Study completed	NA
FGFR mutations	Debio 1347 (REF.[149])	Phase II basket trial (FUZE)	Enrolment ongoing	NA
	TAS-120 (REF.[150])	Phase II basket trial (TiFFANY)	Enrolment ongoing	NA
$KRAS^{G12C}$ mutation	AMG 510 (REF.[131])	Phase I trial in adult patients	$n = 35$; three tumour types: NSCLC ($n = 19$); CRC ($n = 14$); appendix ($n = 2$)	ORR: 17% overall, 50% for NSCLC; CRs: 0%; DCR: 69%; mDOR: NR; mPFS: NR
	MRTX849 (REF.[135])	Phase I trial in adult patients	$n = 17$; four tumour types: NSCLC ($n = 10$); CRC ($n = 4$); appendix ($n = 2$); duodenal ($n = 1$)	ORR: 30% overall, 50% for NSCLC, 25% for CRC; CRs: 0%; DCR: 91%; mDOR: NR; mPFS: NR
NRG1 fusion	Zenocutuzumab[151]	Phase I/II basket trial	Enrolment ongoing	NA
	Tarloxotinib[152]	Phase II basket trial (RAIN)	Enrolment ongoing	NA

CR, complete response; CRC, colorectal cancer; DCR, disease-control rate; DOR, duration of response; m, median; MTC, medullary thyroid cancer; NA, not available; NR, not reported; NSCLC, non-small cell lung cancer; ORR, overall response rate; PFS, progression-free survival; PTC, papillary thyroid carcinoma.
[a]As of 8 February 2020 in clinicaltrials.gov.

Carmagnani Pestana NRCO 2020

Occurrence of co-mutations in oncogene-addicted NSCLC



Skoulidis & Heymach Nat Rev Cancer 2019

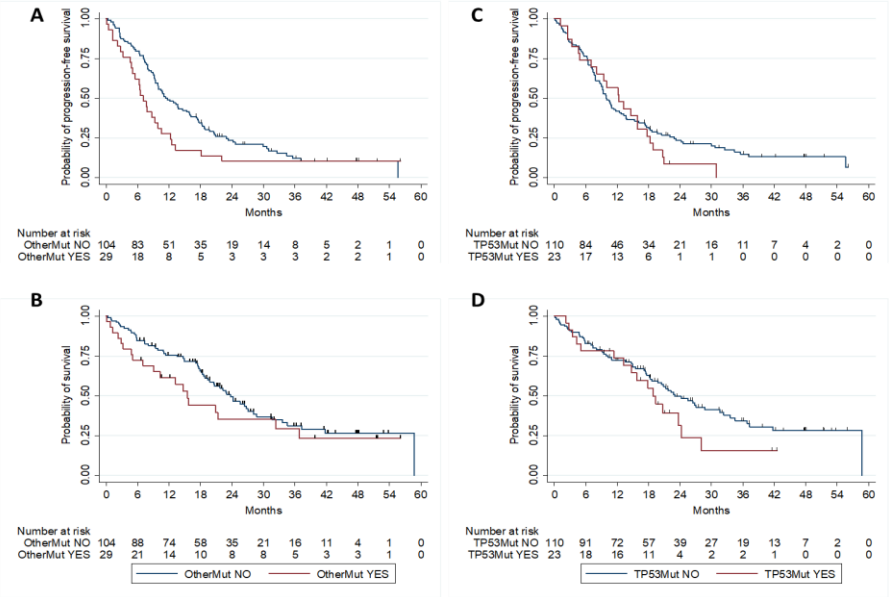
Outcome of EGFR-mutant patients with and without co-mutations

KRAS, NRAS, BRAF, ERBB2, PIK3CA, MET

TP53

PFS

OS



Rachiglio Cancers 2019

Study	Setting	Assay(s)	Number of Patients	Number of Assays	Number of Patients Matched	Match Rate, %[a]	Reference
North America							
MSK-IMPACT	Single-center	DNA: 341- to 410-gene NGS panel (all exons and selected introns)	10,336	10,945	527[b]	11[b]	12
MD Anderson Personalized Cancer Therapy Program	Single-center	DNA: 10-gene NGS panel (hotspot)	1,144	1,144	211	18	13
MD Anderson Personalized Cancer Therapy Program	Single-center	DNA: 11- to 50-gene NGS panel (hotspot)	2,000	2,000	83	4	14
MD Anderson Personalized Cancer Therapy Program	Single-center	DNA: 236 genes	339	339	122	36	15
PREDICT	Single-center	DNA: 182- to 236-gene NGS panel (Foundation Medicine)	347	347	87	25	16
IMPACT/COMPACT	Single-center	DNA: 23- to 50-gene NGS panel (hotspot); Protein: PTEN IHC	1,640	1,640	89	5	17
NCI-MATCH	Multicenter	DNA: 143-gene NGS panel (hotspot); Protein: PTEN, MLH1, MSH2, and Rb IHC	5,540	5,540	686	12	18
Europe							
MOSCATO	Single-center	DNA: 40- to 75-gene NGS panel (hotspot), CGH, WES in limited number of cases; RNA: RNAseq; Protein: MET and phospho-MET IHC	843	843	199	24	19
Asia							
IMPACT-SG	Single-center	DNA: NGS panel (variable number of genes, hotspot); Protein: ALK, cMET, cMYC, FGFR2, HER2, HGF, MMR, NTRK, PTEN, ROS1, and PD-L1 IHC	1,015	1,064	53	5	
IMAC	Single-center	DNA: 50-gene NGS panel (hotspot)	365	365	23	6	20
NEXT 1	Single-center	DNA: 83- to 381-gene NGS panel (hotspot); Protein: PTEN, MET, and HER2 IHC	588	588	60	10	21
TOP-GEAR	Single-center	DNA: 114-gene NGS panel (all exons and selected introns)	187	187	25	13	22
Kyoto University Hospital Study	Single-center	DNA: 215-gene NGS panel (all exons and selected introns)	73	73	9	12	23

Precision Oncology Efforts Across the Globe

Yam JCO Prec Oncol 2021

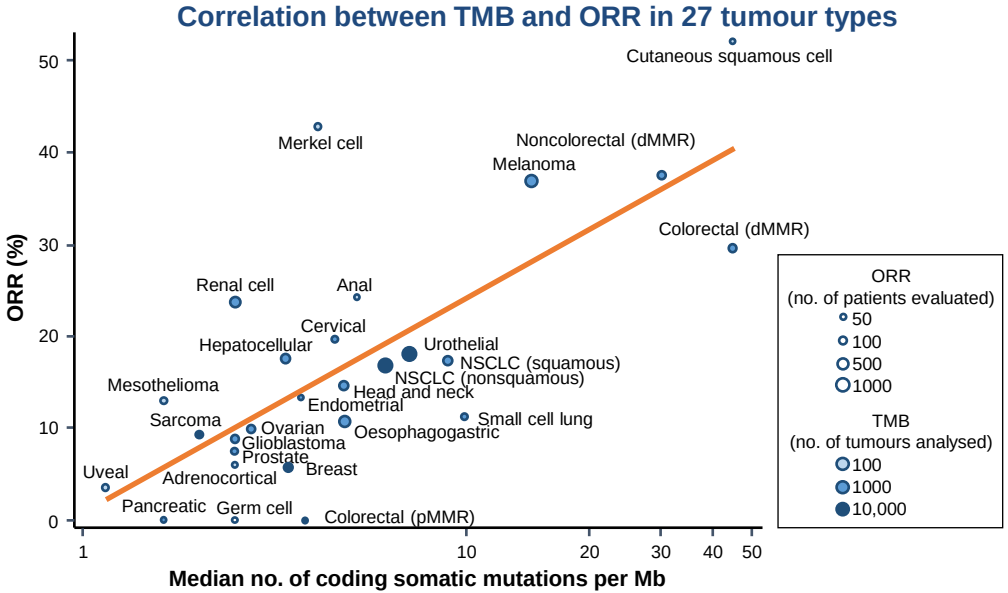
There appears to be significant correlation between TMB and patient response to anti–PD-L1/PD-1 therapy

Investigation overview: literature review to identify data to explore the relationship between TMB and response to anti–PD-L1/PD-1 therapy

Parameters: a literature search yielded studies reporting ORR and studies that met all of these criteria:

- Only monotherapy anti–PD-L1/PD-1 as the treatment
- Minimum of 10 patients enrolled
- PD-L1–positive or –negative patients enrolled

TMB assessment: evaluated using a comprehensive genomic profiling assay provided by Foundation Medicine; defined as the median number of coding somatic mutations



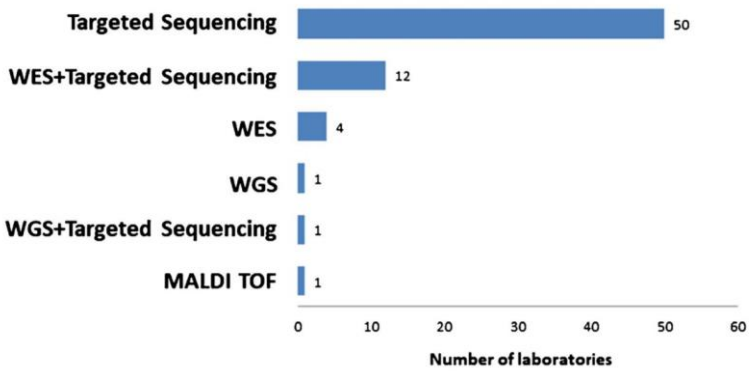
Significant correlation (*P*<0.001) between TMB and ORR was observed

dMMR=mismatch repair deficient; Mb=megabase; no.=number; NSCLC=non-small cell lung cancer; ORR=overall response rate; PD-1=programmed death receptor-1; PD-L1=programmed death ligand 1; pMMR=mismatch repair proficient; TMB=tumour mutational burden.

Yarchoan M et al. *N Engl J Med*. 2017;377(25):2500-2501.

TMB TESTING IN CLINICAL RESEARCH

Methods used for TMB analyses – an IQN Path survey

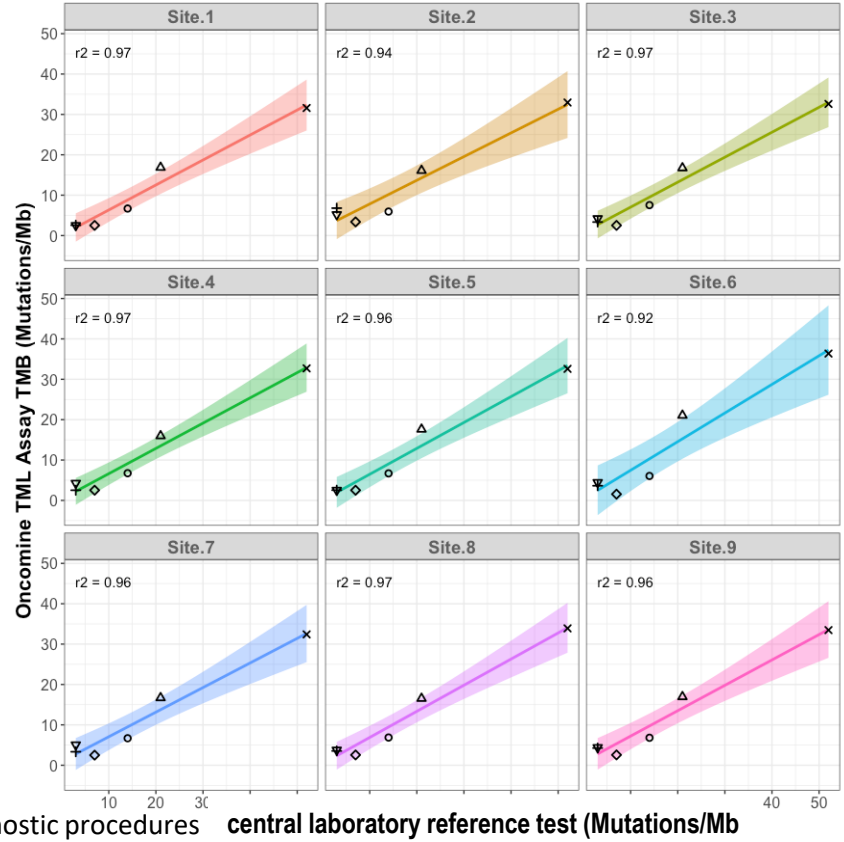


Panel	No. of laboratories
Oncomine™ Tumor Mutation Load	21
Custom panels	18
TruSight™ Oncology 500	6
TruSight™ Oncology 500 + Oncomine™ Tumor Mutation Load	3
Oncomine™ Comprehensive Assay	2
Oncomine™ (not specified)	2
QIAseq™ Tumor Mutational Burden Panel	2
Oseq™-T BGI	2
Oncomine™ Tumor Mutation Load + Oncomine™ Comprehensive Assay	1
TruSight™ Oncology 500 + QIAseq™ Tumor Mutational Burden Panel	1
Oncomine™ Comprehensive Assay + TruSight™ Oncology 500	1
NEOplus™ V2 RUO	1
YyveOne™ Plus	1
Avenio™ Expanded ctDNA	1

IQNPath

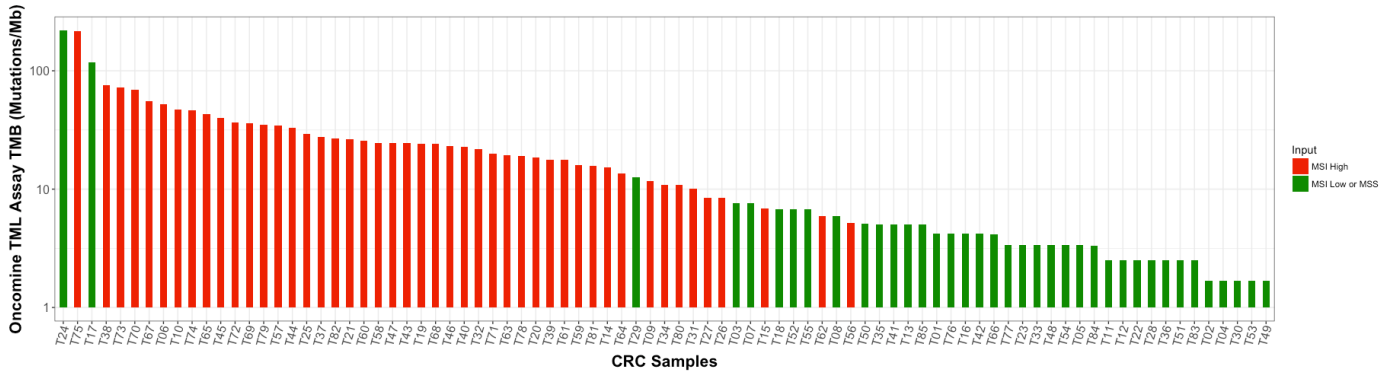
Fenizia Virchows Arc 2021

TMB estimates by Oncomine TML assay on six FFPE samples compared with central laboratory reference test values



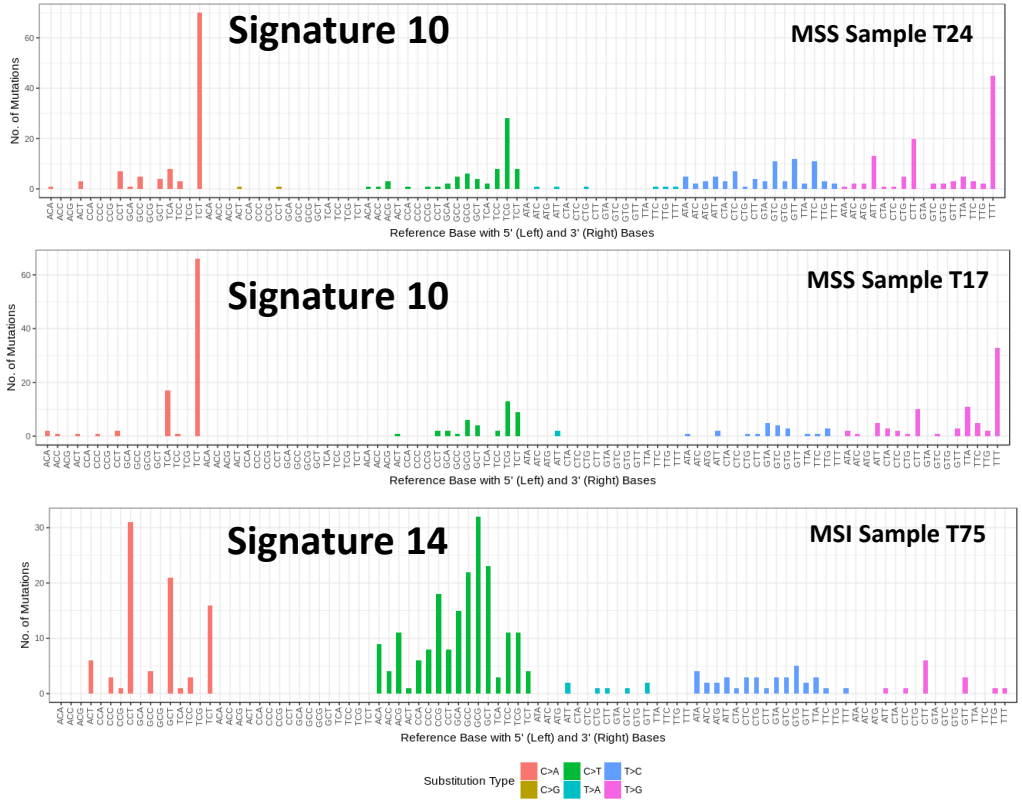
Fenizia J Mol Diag 2021

Distribution of TMB values on CRC samples



Fenizia J Mol Diag 2021

Substitution type and context of somatic mutations of three highest TMB value samples



- Signature 10: observed in altered activity of POLE gene
- Signature 14: linked to defects in mismatch repair

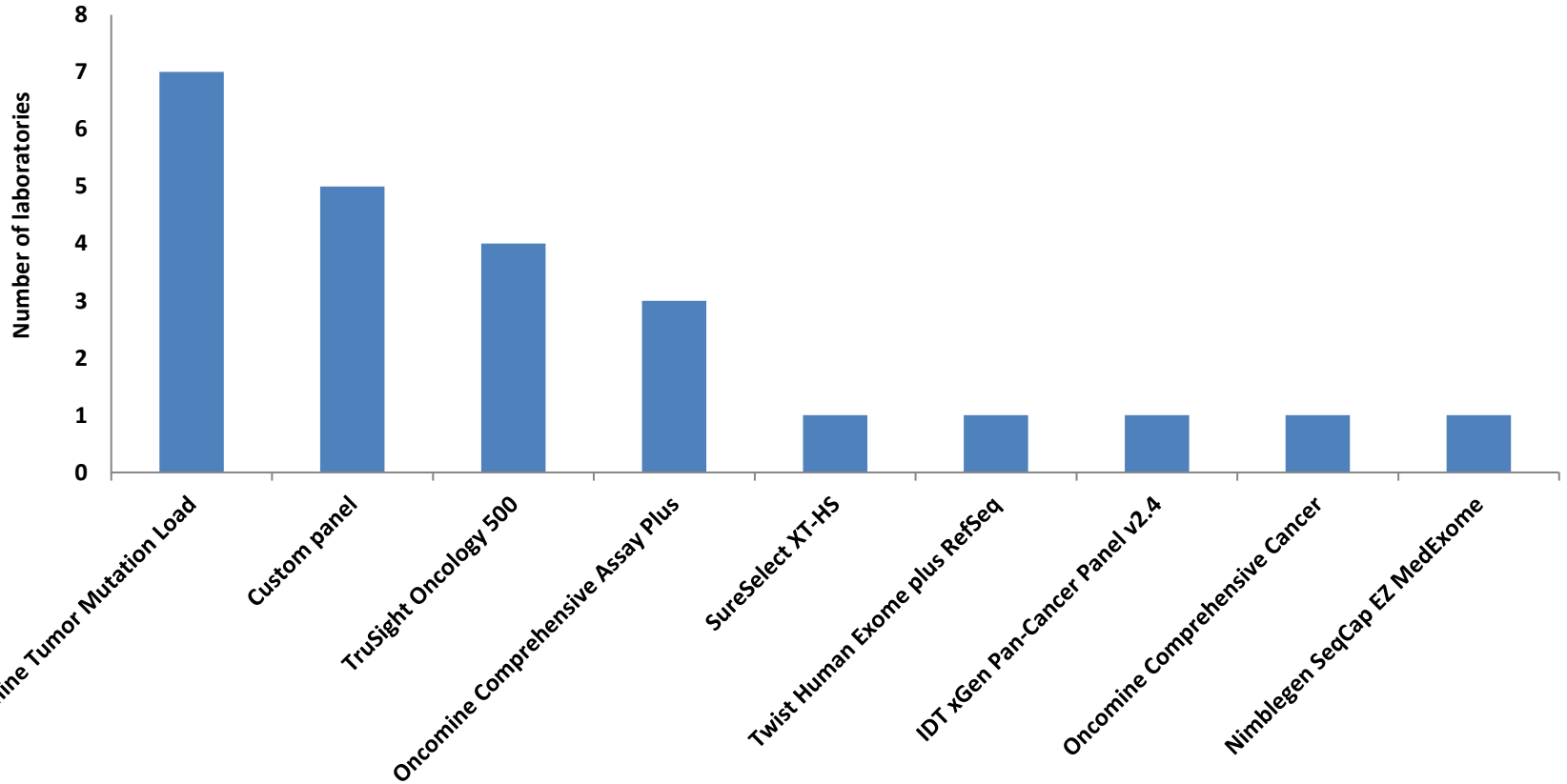
Fenizia J Mol Diag 2021

Results of pilot EQA scheme for TMB

	N°
Centers registered to the scheme	29
Centers that submitted TMB results	23
Centers that did not submitted results due to absence of normal samples	2
Centers that did not submit the results without any explanation	4

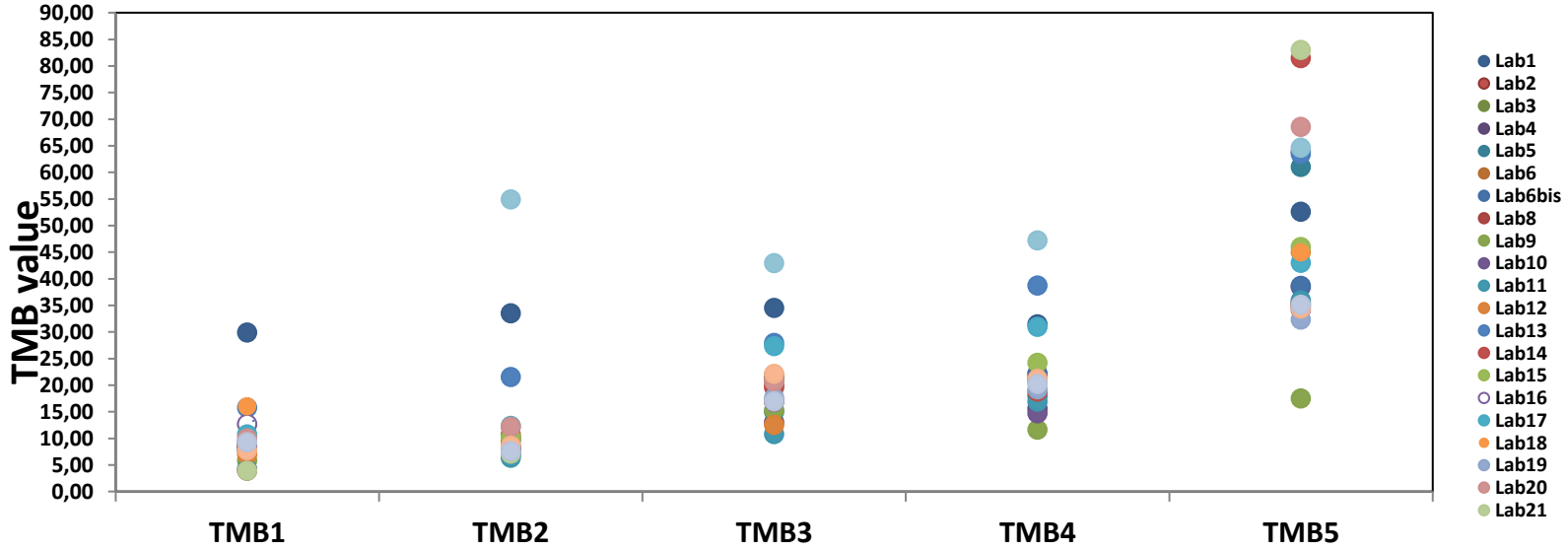
IQNPath

NGS panel used to assess TMB



IQNPath

TMB results on different EQA samples



	Lab1	Lab2	Lab3	Lab4	Lab5	Lab6	Lab6bis	Lab8	Lab9	Lab10	Lab11*	Lab12	Lab13	Lab14	Lab15	Lab16	Lab17	Lab18	Lab19	Lab20	Lab21	Lab22	Lab23*	Lab24	FMI
TMB1	29,90	9,29	8,57	7,8	4	8,59	8,04	ND	5,82	8,62	4,25	7	15,77	3,9	12,56	12,71	10,74	15,99	9,2	10	3,9	7,78	ND	9,27	10,09
TMB2	33,51	7,61	9,54	8,50	7	10,74	6,92	10	10,19	8,11	6,36	ND	21,51	7,8	10,03	7,60	12,36	7,59	7,53	12,14	7,10	8,61	54,90	7,58	5,04
TMB3	34,54	16,96	21,95	13,00	15	21,01	17,13	20	15,29	21,30	10,81	12,50	27,96	19,6	20,91	16,85	27,36	16,81	17,60	20,71	ND	22,1	42,93	16,97	13,87
TMB4	31,44	21,10	20,83	15,60	18	22,06	22,16	ND	11,65	14,70	16,92	21	38,71	18,8	24,22	20,99	30,94	20,22	19,23	20,71	20,40	21,16	47,21	20,23	15,13
TMB5	52,58	35,34	35,65	38,50	61	34,6	38,66	35	17,48	63,90	35,94	45	63,44	81,5	45,99	34,16	42,98	44,98	32,32	68,57	83	34,4	64,66	35,12	69,35

IQNPath

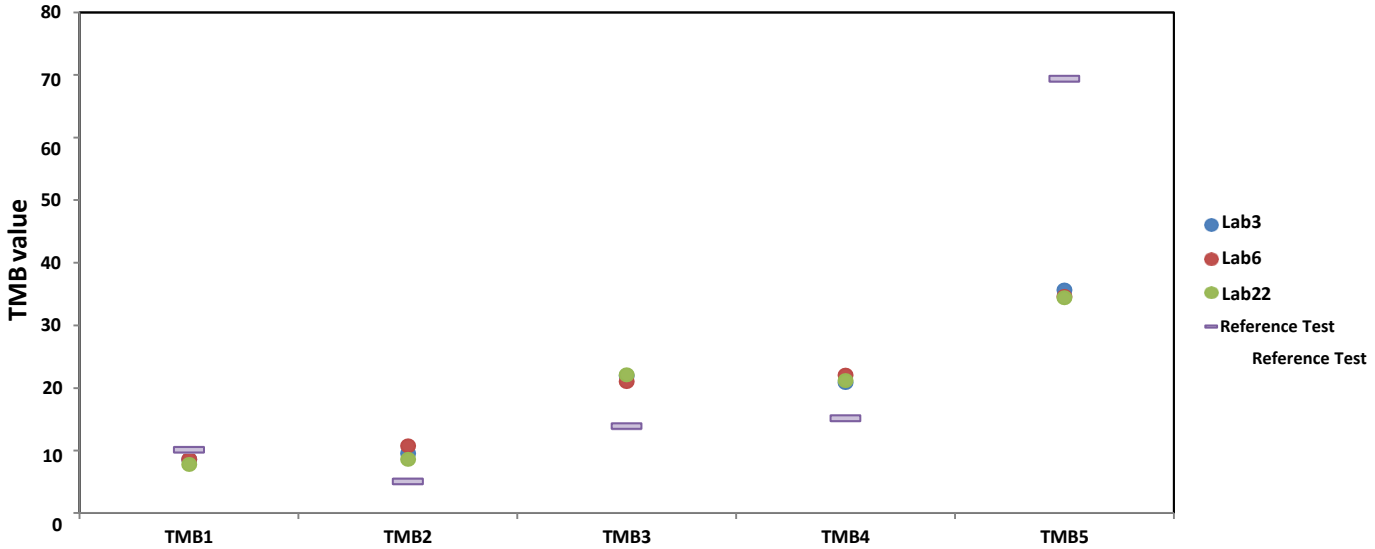
*: TMB assessed with Whole Exome Sequencing; central laboratory reference test I:; ND: TMB value not determined

TMB results on different EQA samples with OTML

Non synonymous only	TMB1	TMB2	TMB3	TMB4	TMB5
Lab2	9,29	7,61	16,96	21,1	35,34
Lab6bis	8,04	6,92	17,13	22,16	38,66
Lab19	9,2	7,53	17,6	19,23	32,32
Lab24	9,27	7,58	16,97	20,23	35,12
Std	0,53	0,28	0,26	1,08	2,25
Non synonymous and synonymous	**TMB1**	**TMB2**	**TMB3**	**TMB4**	**TMB5**
Lab16	12,71	7,6	16,85	20,99	34,16
Lab17	10,74	12,36	27,36	30,94	42,98
Lab18	15,99	7,59	16,81	20,22	44,98
Std	2,16	2,24	4,96	4,88	4,70
Validation phase	9,24	7,54	16,81	19.31	36,23
Reference Test	10,09	5,04	13,87	15,13	69,35

IQNPath

TMB results on different EQA samples with OCA plus



	TMB1	TMB2	TMB3	TMB4	TMB5
Lab3	8,57	9,54	21,95	20,83	35,65
Lab6	8,59	10,74	21,01	22,06	34,6
Lab22	7,78	8,61	22,1	21,16	34,4
Std	0,38	0,87	0,48	0,52	0,55
Reference Test	10,09	5,04	13,87	15,13	69,35

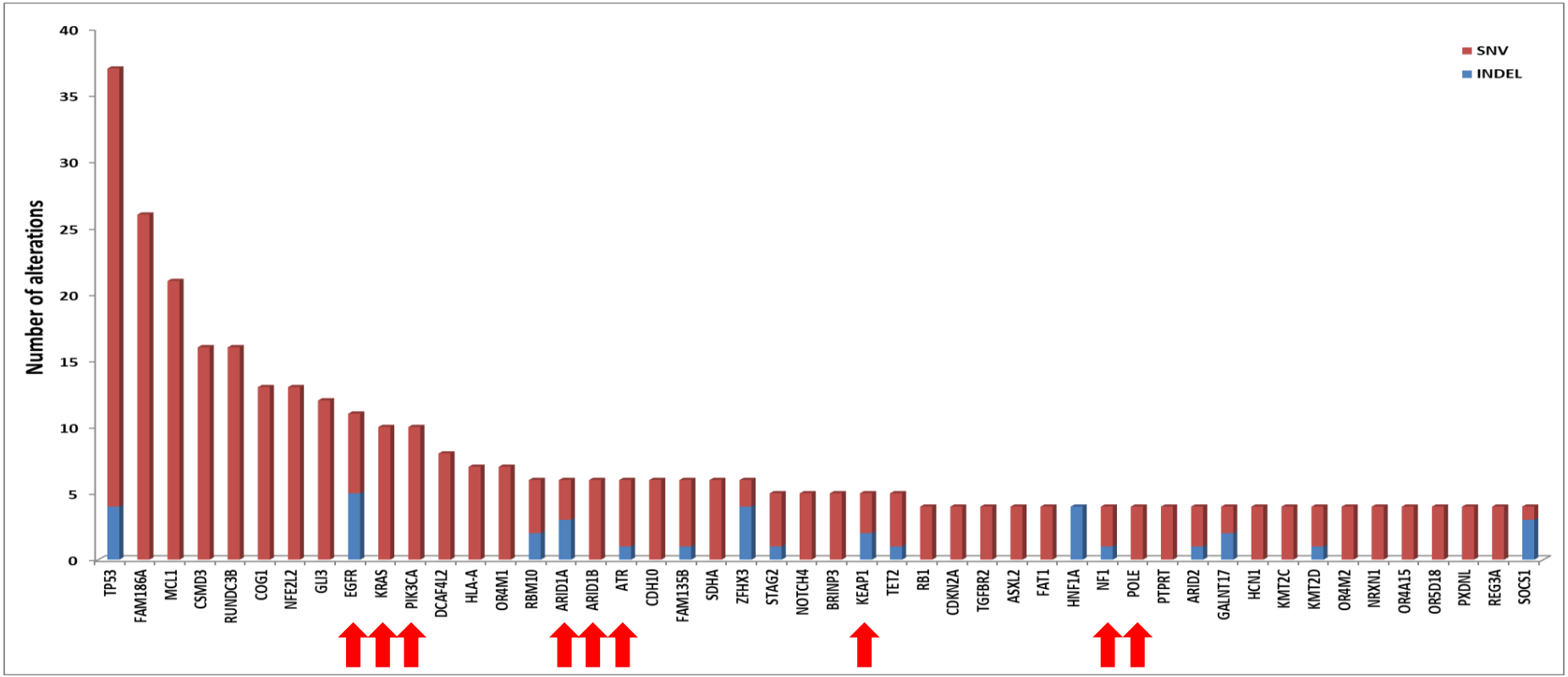
IQNPath

Statistical description of NSCLC samples tested with central laboratory reference test and OCA Plus

	Total (N=53)
Reference Test	
Mean (SD)	10.1 (8.56)
Median [Min, Max]	7.57 [0, 35.3]
thermo	
Mean (SD)	12.0 (5.85)
Median [Min, Max]	10.4 [2.86, 32.7]

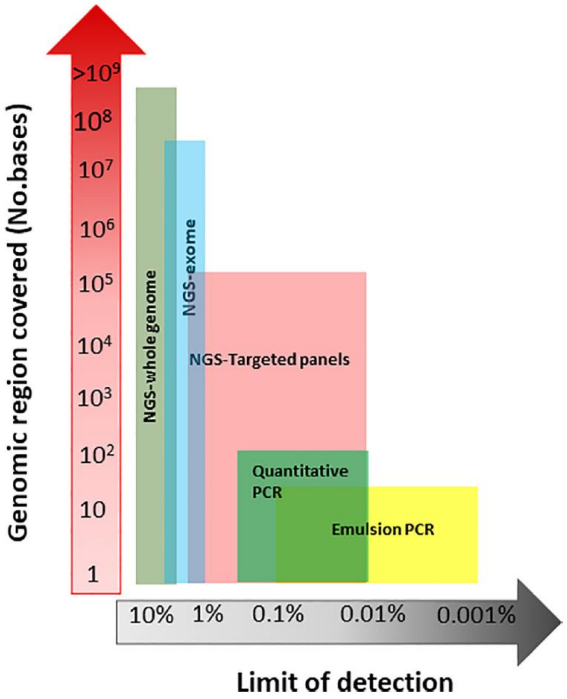
Genetic variants identified in NSCLC with OCA Plus

In 58 NSC:C clinical research samples, 721 genomic alterations in 293 genes were observed



cfDNA ANALYSIS IN CLINICAL RESEARCH

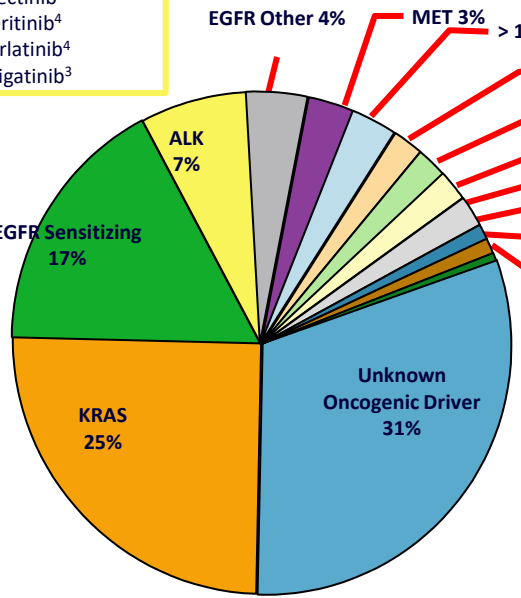
Analytical Sensitivity of the Different Approaches Used for cfDNA Analysis



- Methods based on quantitative PCR have a limit of detection (LoD) up to 0.005%
- The Emulsion PCR-based technologies [Droplet Digital PCR (ddPCR) and Beads, Emulsion, Amplification, and Magnetics (BEAMing)] have a LoD ranging from 0.01 to 0.001%
- Technologies based on quantitative PCR and emulsion PCR can analyze up to hundreds bases and interrogate a limited number of loci, usually up to 10
- Massively parallel or next-generation sequencing (NGS) technologies allow sequencing from 200 Kb to 3.2 Gb with a sensitivity up to 0.01% for targeted panels

Normanno CTR 2018

Targeted therapy for lung adenocarcinoma - 2021



MET ex14 Skip
- Crizotinib[4]
- Capmatinib[4]
- Tepotinib[4]
- Cabozantinib[2]

HER2
- Trastuzumab emtansine[2]
- T-DXd (DS-8201a)[2]
- Afatinib[2]
- Dacomitinib[2]

ALK
- Crizotinib[4]
- Alectinib[4]
- Ceritinib[4]
- Lorlatinib[4]
- Brigatinib[3]

EGFR Sensitizing
- Gefitinib[4]
- Erlotinib[4]
- Afatinib[4]
- Osimertinib[4]
- Necitumumab[4]
- Dacomitinib[4]
- Rociletinib[3]

ROS1
- Crizotinib[4]
- Cabozantinib[2]
- Ceritinib[2]
- Lorlatinib[2]
- DS-6051b[1]

BRAF
- Dabrafenib+ Trametinib[4]

RET
- Selpercatinib[4]
- Pralsetinib[4]
- Cabozantinib[2]
- Alectinib[2]
- Apatinib[2]
- Vandetanib[2]
- Ponatinib[2]
- Lenvatinib[2]

KRAS G12C
- AMG-510[2]
- MRTX849[2]

PIK3CA
- LY3023414[2]
- PQR 309[1]

MEK1
- Trametinib[2]
- Selumetinib[3]
- Cobimetinib[1]

NTRK1
- Entrectinib[4]
- Larotrectinib[4]
- Cabozantinib[2]
- DS-6051b[1]

Key

1. Phase I
2. Phase II
3. Phase III
4. Approved

Modified from Tsao AS, J Thorac Oncol. 2016

Sensitivity and specificity of cfDNA testing with the Oncomine Lung cfTNA Assay

- Anaysis of plasma-derived cfDNA from 107 metastatic NSCLC patients with the Oncomine Lung cfTNA Assay
- 2/77 EGFR FP and 5/81 KRAS FP
- 2 KRAS FP in 30 EGFR mutant patients
- All NGS FP calls confirmed by ddPCR on cfDNA

Gene	EGFR	KRAS
Sensitivity	76.7%	61.5%
Specificity	97.4%	93.8%
PPV	92%	76.2%
NPV	91.5%	88.4%
Concordance	91.6%	86%

Pasquale TLCR 2020

CURRENT STATUS OF BIOMARKER TESTING IN EUROPE

IQN Path - EFPIA - ECPC project: “Organization and quality of biomarkers testing in Europe”

- Biomarker testing has become a critical tool to ensure the optimal delivery of care for cancer patients
- However, across Europe, access to high quality biomarker tests is inconsistent

- IQN Path, EFPIA and ECPC have decided to work together to address the challenges of biomarker testing in collaboration with pharma and laboratory partners to ensure that
  - **Biomarker testing is readily available to all cancer patients**
  - **There is a system in place to ensure emerging biomarker tests are rapidly available**
  - **Testing quality is high**
- The project is organized in two phases:
  - **To map the current status of biomarker testing in 27 EU countries and UK**
  - **To develop policy recommendations that will be presented at the EU level**

efpia IQNPath International Quality Network for Pathology European Cancer Patient Coalition

Access to and quality of 12 biomarker tests plus liquid biopsy in Europe

Methodology

Biomarker tests

Tier 1
Single gene IHC / FISH
PD-L1
Single gene molecular
BRCA
EGFR
NTRK
Complex genomic signatures
NGS hotspot (up to 50 genes) / targeted panel
NGS comprehensive panel

Tier 2
Single gene IHC / FISH
HER2
ALK
MMR / MSI
ROS1
Single gene molecular
BRAF
KRAS / NRAS
Other
Liquid biopsy *(ctDNA / plasma)*

Geographical coverage

Core countries

EU4 / UK

- Germany
- France
- UK
- Spain
- Italy

Ex-EU4 / UK

- Belgium
- Netherlands
- Sweden
- Poland
- Greece

Scope: *coverage of Tier 1 & 2 tests*

Remaining countries

Western Europe

- Austria
- Ireland
- Luxembourg

Nordics

- Denmark
- Finland

Central Europe

- Bulgaria
- Croatia
- Czech Republic
- Hungary
- Romania
- Slovenia
- Slovakia

Southern Europe

- Cyprus
- Malta
- Portugal

Baltics

- Estonia
- Latvia
- Lithuania

Scope: *coverage of Tier 1 tests only*

Current biomarker testing landscape for each country based on agreed access and quality metrics

Methodology

Drug access – focused on precision medicines

Drivers	Factors to consider
Drug availability	• *Drug availability (approval and commercial launch)* • *Level of drug reimbursement by public payers*

Test access drivers

Drivers	Factors to consider
Laboratory access	• *Laboratory capabilities & penetration* • *Infrastructure to support sample flow (e.g. sample origination)*
Test availability	• *% of laboratories with in-house capabilities or sending out tests to partner labs* • *Total time test has been available for*
Test reimbursement	• *Level of public reimbursement*
Test order rate	• *Patients tested / patients eligible*

Test quality drivers

Drivers	Factors to consider
Quality scheme participation	• *EQA scheme participation*
Laboratory accreditation	• *Proportion of laboratories with ISO accreditation*
Test turnaround time	• *Time from test order to receipt of results*

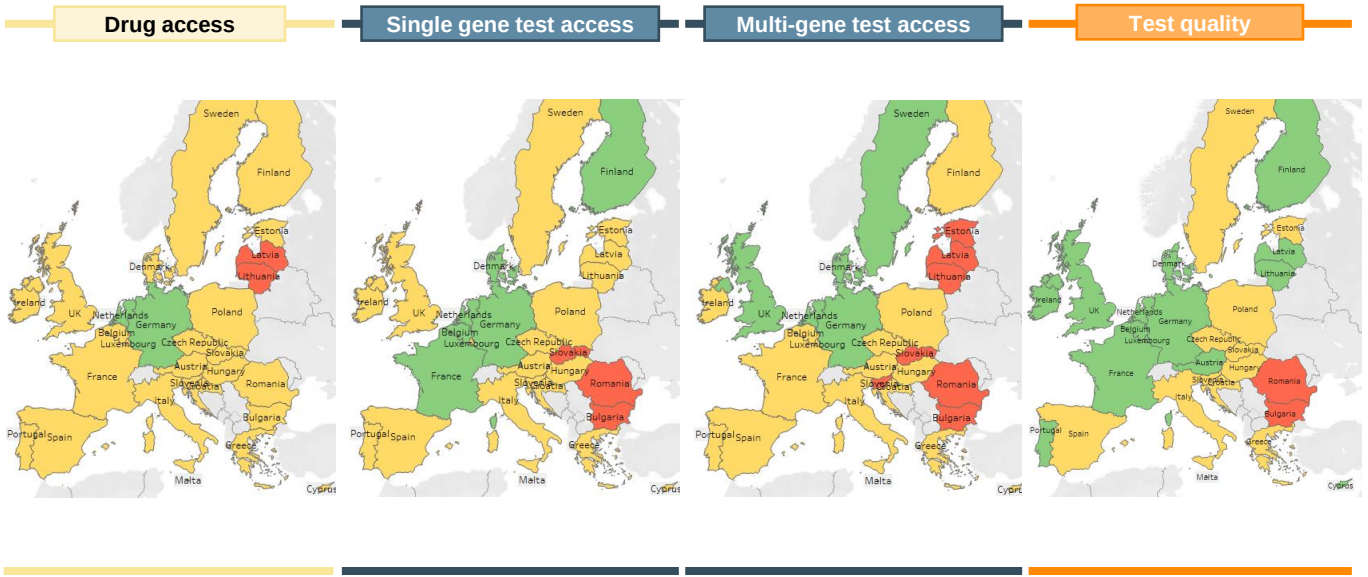
Access metric

Quality metric

Source: L.E.K. research and analysis

The research shows significant variations in drug and test access as well as test quality across Europe

Summary of findings



Key:

High	Medium
Low	N/A

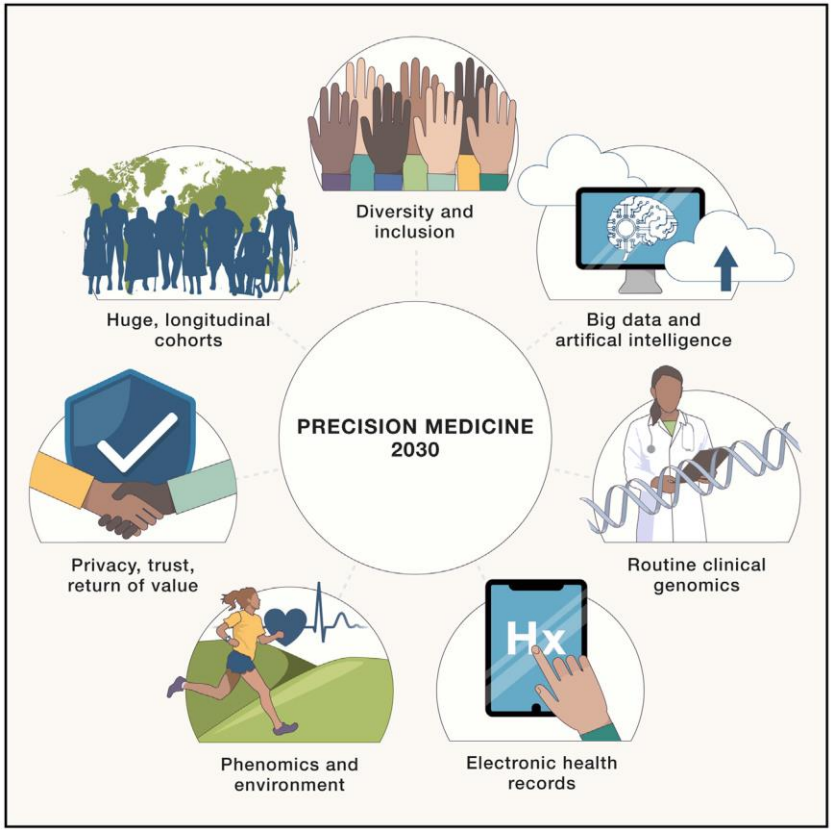
Note: Drug access scores derived from the total number of reimbursed precisions drugs per country; both single gene and multi-gene test access sores are composite scores of lab access, time for which given test has been available, test availability, percentage public reimbursement of testing, and order rates; Test quality is a combined score of EQA participation, ISO accreditation, and turnaround time (for both single gene and multi-gene tests)
Source: IQN Path / EFPIA Lab manager survey (2020); L.E.K. research and analysis

Key barriers to high quality biomarker testing to overcome

Summary of findings

Key metrics investigated over the course of the project	*Key barriers*
Precision medicine availability *Is there a linked therapy available and publicly reimbursed to drive testing?*	▪ Significant delay in medicines access following EMA approval triggering a lag in biomarker test access ▪ Some precision medicines launched but not reimbursed
Biomarker test infrastructure *Do the capabilities exist in labs to perform testing of all focus biomarkers?* *For NGS, is the infrastructure (e.g. data sharing) in place to support use?*	▪ Regional variations in diagnostic lab coverage ▪ Variation in or lack of availability of different test technologies / capabilities (e.g., NGS, FISH) or of the ability to perform different biomarker tests
Approval and integration of tests *Is there a pathway to support the timely introduction of new tests?*	▪ No / weak link between regulatory and reimbursement approval process for precision medicines and the relevant biomarker test(s) resulting in delays ▪ Slow integration of new biomarker tests into SoC
Test funding and reimbursement *Is a public funding mechanism in place to support reimbursement? How is the transition from pharma to public funding managed?*	▪ Funding not sufficient to support development of testing capability / infrastructure across regions or support widespread biomarker testing ▪ Consistency in level and timing of reimbursement hindered by patchwork of funding sources ▪ Lack of funding to support transition to larger gene panel tests
Test uptake and continued use *Is there widespread awareness of available tests and of referral pathways?* *Is there clarity on the reimbursement process?*	▪ Low awareness of availability and referral pathways new tests / tech ▪ Lack of centralisation of biomarker data, limiting the uptake / utility of large panel testing
Test quality *Is testing carried out to a sufficiently high standard?* *What system / measures are in place to drive quality assurance and fast turnaround times?*	▪ Lack of participation in EQA schemes often driven by budget limitations ▪ Limited ISO accreditation in a number of countries ▪ High send-out rates impact turnaround times

Seven opportunities for precision medicine by 2030



Denny & Collins Cell 2021

Genomics and clinical research in Europe: a call to action

- Comprehensive genomic profiling can significantly improve the implementation of precision oncology in clinical research
- Prospective studies of comprehensive genomic profiling in European academic centers are essential to allow access to novel therapeutics through clinical trials
- Regional/national reference centers for the execution of complex genomic analyzes should be created in all European countries
- Investments are needed in crucial sectors such as bioinformatics and artificial intelligence to integrate different omics information with clinical, environmental, family and lifestyle factors

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- The European Federation of Pharmaceutical Industries and Associations (EFPIA)
- IQN Path