CIRCULATING CELL FREE NUCLEIC ACID: FROM BLOOD TO BIOMARKER

Robyn Marshall

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NEXT GENERATION DIAGNOSTICS

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- Speaker was provided travel and hotel support by Thermo Fisher Scientific for this presentation, but no remuneration

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Introduction

- Biomarker testing
- Cell free nucleic acid into the realm of clinical testing
- Oncomine™ research assay principles
- Oncomine™ research assay interpretation
- Clinical implications and reporting
- Other biomarkers to consider in solid tumors

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Future potential roles for Biomarkers in helping to answer

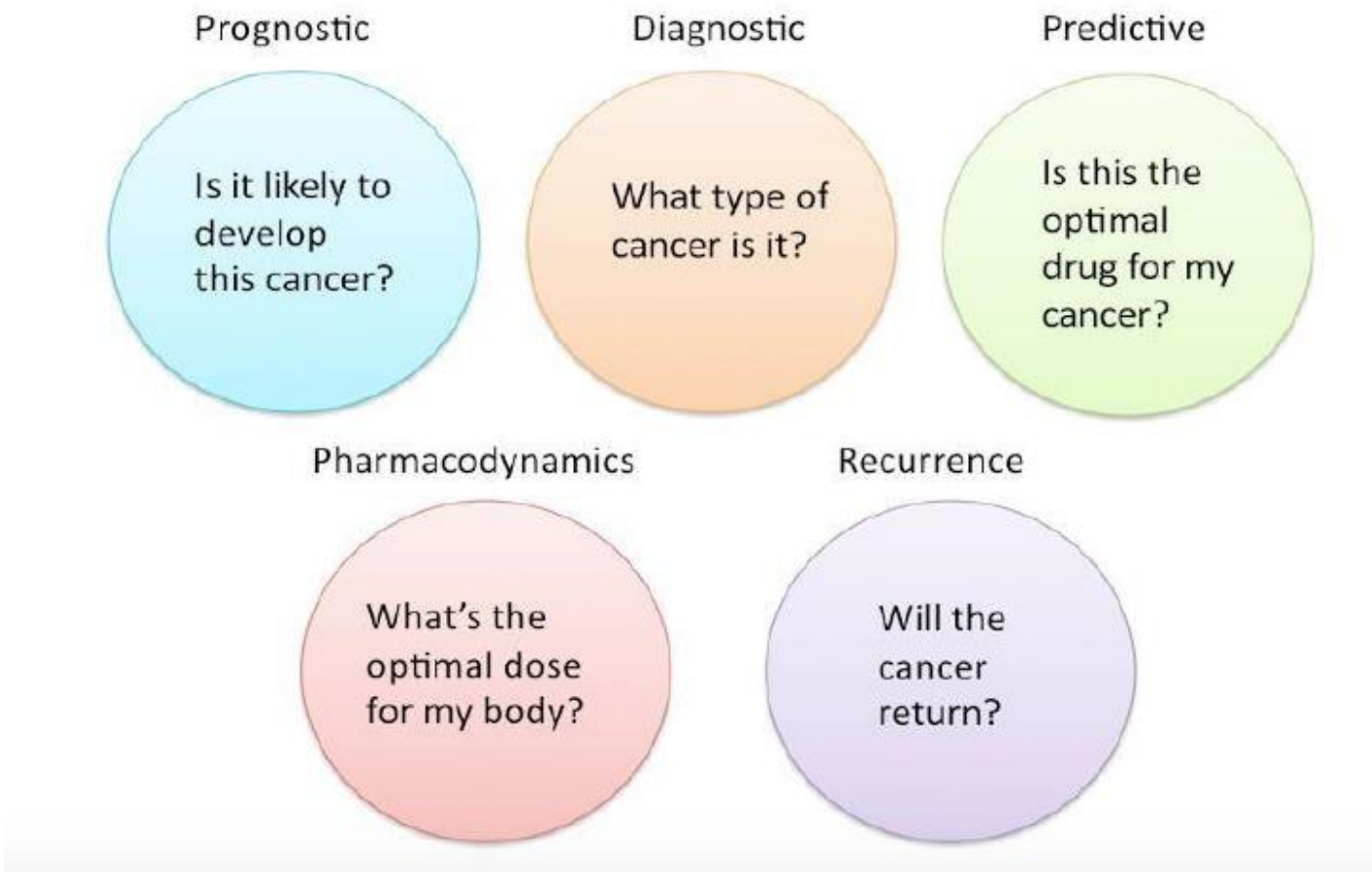

Image courtesy of Dr Philip Jermann, Basel

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Tissue biopsy and biomarkers research testing

- ***Tissue biopsy samples*** are widely used to characterize tumours but the applications are limited
  - tissue availability
  - sampling frequency
  - genetic heterogeneity

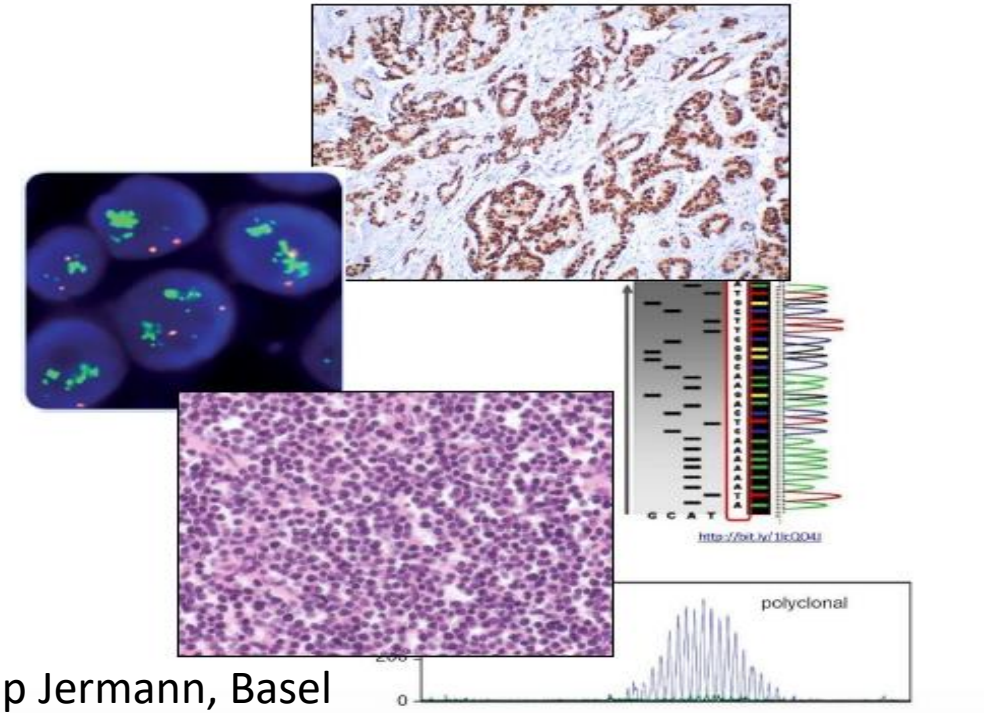

Image courtesy of Dr Philip Jermann, Basel

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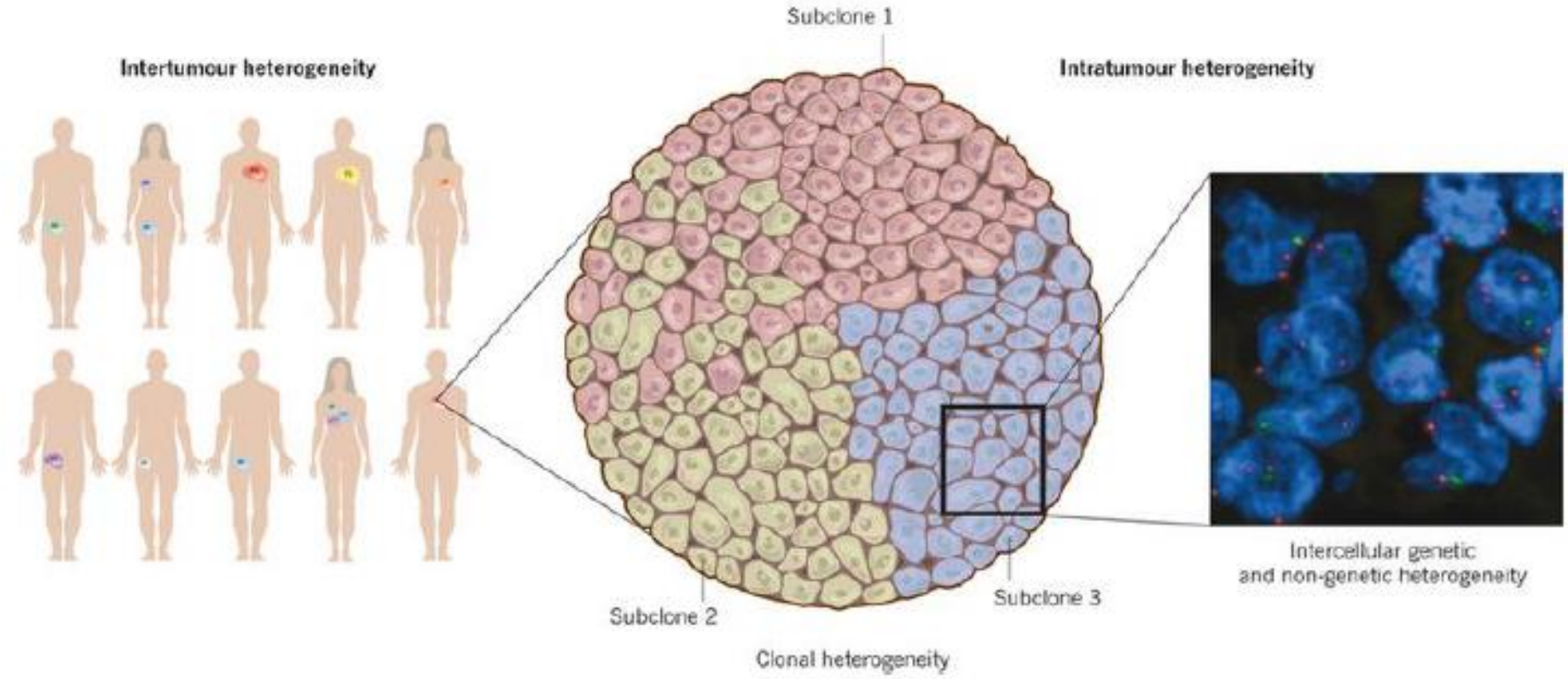
Tumour tissue heterogeneity



Burrell et al. The Causes and Consequences of Genetic Heterogeneity in Cancer Evolution, Nature, 2013

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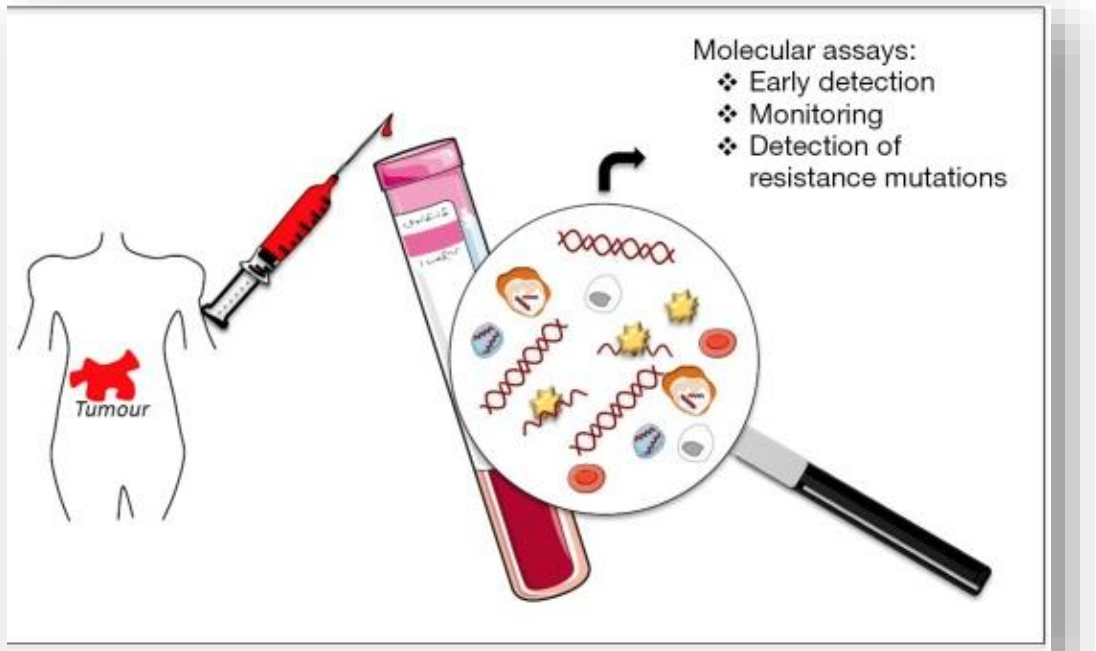
Cell-free NA

- Circulating cfNA, commonly named "**liquid biopsy**", has emerged as a new promising ***non-invasive*** tool to detect biomarkers in several cancer research studies while bypassing the problem of tumour heterogeneity and ease of access to sample



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Nucleic acid present in plasma

- **miRNA**

  Small 18-24nt RNA wrapped in a large complex of proteins

- **Exosomes**

  Microvesicles of about 50-100nm exocytosed from cells; contain miRNA and mRNA

- **Circulating cell-free DNA (cfDNA)**

  Fragmented non-encapsulated DNA of about 170bp; rapidly degraded

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Origins of cfDNA

- **Necrosis**
  - Caused by factors external to the cell
  - Infection, toxins, trauma
  - Cell contents are released
  - DNA degrades into nucleosomal units

- **Apoptosis**
  - Programmed cell death
  - Cell fragments into apoptotic bodies, which are digested by phagocytes
  - Very little DNA released

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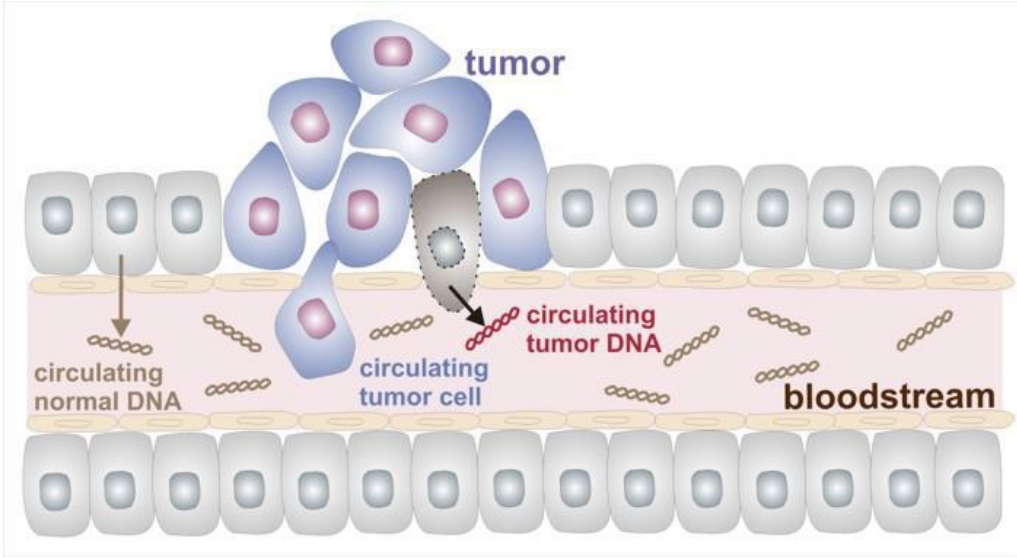
Potential future utility of cfDNA assays

- Treatment decisions with regards to targeted drugs and therapies
- Relapsed, progressive or advanced disease
- May overcome tumour heterogeneity / sampling error*
- Prognosis prediction
- Acquired resistance
- Response to treatment
- Currently four research assays:
  - cfDNA Lung
  - cfDNA Breast
  - cfDNA Colon
  - cfTNA Pan-cancer
- Out of scope for cfDNA assay research
  - Screening
  - Newly diagnosed cancer where tissue is available*
  - Early stage cancer – likelihood of false negatives greatly increased*
  - Genetic susceptibility screening
  - New drug or target discovery
  - Advanced or relapsed/refractory disease where tissue is available*



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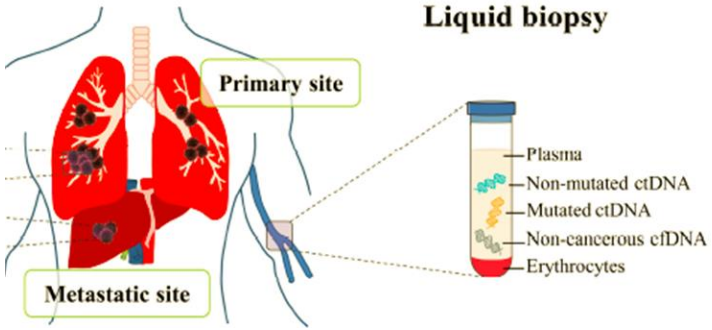
Advantages of cfDNA

- ***Homogeneity*** of plasma cfDNA
- Ability to take **blood samples at various timepoints** to enable multiple/repeat samples and time-course potentially enables:
  - Earlier detection
  - More samples from more patients
  - Detect actionable mutations
  - Changes in mutation levels over time
- Ability to detect ***secondary cancers*** by biomarkers



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‘Research studies highlighting potential application of cfNA testing in Oncology research’

A comparison of *EGFR* mutation status in tissue and plasma cell-free DNA detected by ADx-ARMS in advanced lung adenocarcinoma patients

Hanyan Xu[1#], Adam Abdul Hakeem Baidoo[1#], Shanshan Su[1], Junru Ye[1], Chengshui Chen[1], Yupeng Xie[1], Luca Bertolaccini[2], Mahmoud Ismail[3], Biagio Ricciuti[4], Calvin Sze Hang Ng[5], Raja M. Flores[6], Yuping Li[1]; written on behalf of AME Lung Cancer Collaborative Group

Transl Lung Cancer Res 2019

Concordance between genomic alterations assessed by next-generation sequencing in tumor tissue or circulating cell-free DNA

Young Kwang Chae[1,2,3,*], Andrew A. Davis[2,*], Benedito A. Carneiro[1,2,3], Sunandana Chandra[1,2,3], Nisha Mohindra[2,3], Aparna Kalyan[1,2,3], Jason Kaplan[1,2,3], Maria Matsangou[1,2,3], Sachin Pai[1,3], Ricardo Costa[1,3], Borko Jovanovic[2,3], Massimo Cristofanilli[1,2,3], Leonidas C. Platanias[1,2,3,4], Francis J. Giles[1,2,3]

Oncotarget, 2016

Guide to detecting epidermal growth factor receptor (*EGFR*) mutations in ctDNA of patients with advanced non-small-cell lung cancer

Nicola Normanno[1], Marc G. Denis[2], Kenneth S. Thress[3], Marianne Ratcliffe[4] and Martin Reck[5]

Oncotarget, 2017

Orthogonal Comparison of Four Plasma NGS Tests With Tumor Suggests Technical Factors are a Major Source of Assay Discordance

Daniel Stetson, MS[1]; Ambar Ahmed, MS[1]; Xing Xu, PhD[2]; Barrett R.B. Nuttall, MS[1]; Tristan J. Lubinski, PhD[1]; Justin H. Johnson[1]; J. Carl Barrett, PhD[1]; and Brian A. Dougherty, PhD[1]

JCO Precis Oncol. 2019

Liquid biopsy in colon cancer: comparison of different circulating DNA extraction systems following absolute quantification of *KRAS* mutations using Intplex allele-specific PCR

Vera Kloten[1], Nadine Rüchel[1], Nadina Ortiz Brüchle[1], Janina Gasthaus[1], Nils Freudenmacher[1,2], Florian Steib[1], Jolein Mijnes[1], Julian Eschenbruch[1], Marcel Binnebösel[3], Ruth Knüchel[1] and Edgar Dahl[1,2]

Oncotarget, 2017

Next-generation sequencing in liquid biopsy: cancer screening and early detection

Ming Chen* and Hongyu Zhao

Human Genomics, 2019

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Performance variables

- Limit of detection
  - Very low levels of circulating tumour nucleic acid (ctNA)
  - Blood contamination may easily cause false negatives
  - Early / small tumours may not shed enough ctNA for detection
  - Larger sample volumes than usual
- Release of cellular / leucocyte NA
  - Incorrect storage or collection of samples
  - EDTA – 2 hours from collection to processing
  - Streck – 48 hours from collection to processing
  - Specialised equipment for separation and extraction of ctNA
- Type of assay
  - Capture PCR and Sanger sequencing
  - ddPCR
  - Next generation sequencing

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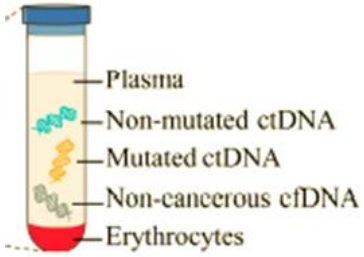
Biological Limitations of cfDNA Analyses



10 mL blood ≅ **20** ng cfDNA ≅ **6** mutant molecules present at 0.1%

Biological limit of detection with cfDNA template

Limit of Detection	1%	0.1%	0.05%
cfDNA (ng)	1	20	30
Mutant Molecules	3	6	4-5
"Usable" Mutant Molecules	1-2	3	2

*Below 0.05%, there may not be any molecules present for analysis even with large input amounts

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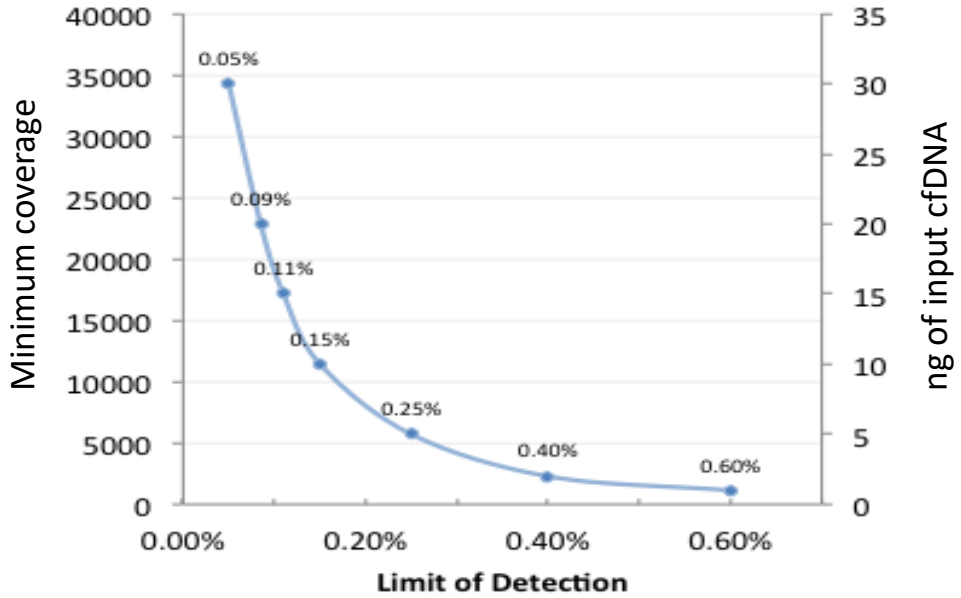
Cancer NGS Research Screening Panels

- Purified DNA is amplified by multiplex PCR for library preparation followed by NGS
- Hundreds of primer sets to detect a wide range of mutations.
- Sensitivity depends on the system used, but can be anywhere from 5% to less than 0.1% frequency of mutation detected.



1 ng cfDNA–0.6% LOD
5 ng cfDNA–0.25% LOD
10 ng cfDNA–0.15% LOD
20 ng cfDNA–0.1% LOD
30 ng cfDNA–0.05% LOD

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Oncomine™ research platform concordance

Sample	Variant	FFPE	cfDNA
1	*EGFR*-L858R	**71.42%**	**2.62%**
2	*TP53*-R158L	**51.89%**	**4.32%**
3	*MET*-T1010I	43.87%	51.75%
	KRAS-G12C	**34.62%**	**0.28%**
4	NA	Not detected	Not detected
5	*EGFR*-L858R	**58.44%**	**7.28%**
	MET-T1010I	41.93%	48.72%
	TP53-Y220C	**35.54%**	**1.93%**
6	*TP53*-R158L	**10.19%**	**1.26%**

Bold numbers indicate allele frequencies as determined using the Oncomine Lung cfDNA Assay for the indicated somatic variants. Non-bold numbers show frequencies of germline variants that were also detected in the targeted libraries.

Ion Torrent Application Note COL03101

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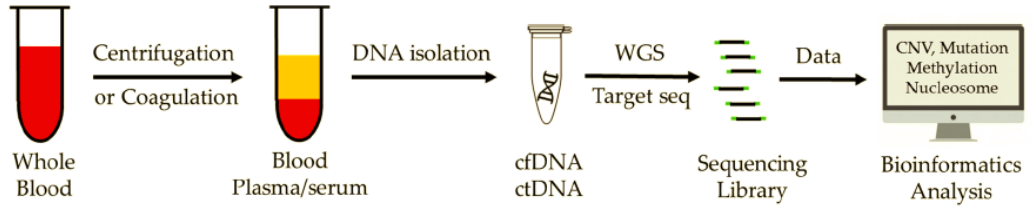
Oncomine™ research platform



- First next-generation sequencing platform approved as companion diagnostics by FDA – Thermo Fisher
- Assay designed specifically for use with ctNA
  - PCR enrichment of very short fragmented ctNA
  - Bead capture and droplet PCR using automated technology
  - Sequencing performed on Ion Torrent platform
  - 2 000 000x coverage of each locus (cf. 2000x for tissue samples)
  - Limit of detection 0,1%
- Bioinformatics
  - Designed specifically for detecting low frequency variants such as found in cell-free assays
  - Access to treatment guidelines and clinical trials

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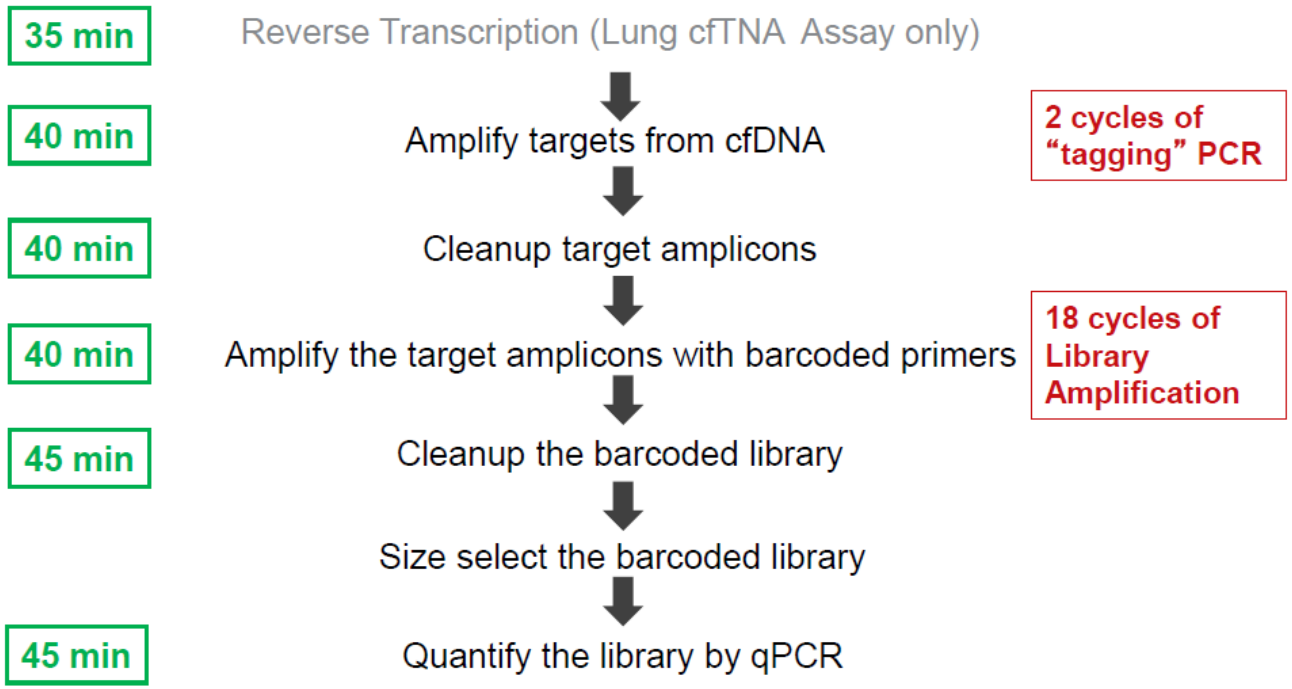
Library Construction Workflow cfTNA



Make 1-8 libraries in 96-well plate format in **3.5- 4 hours**

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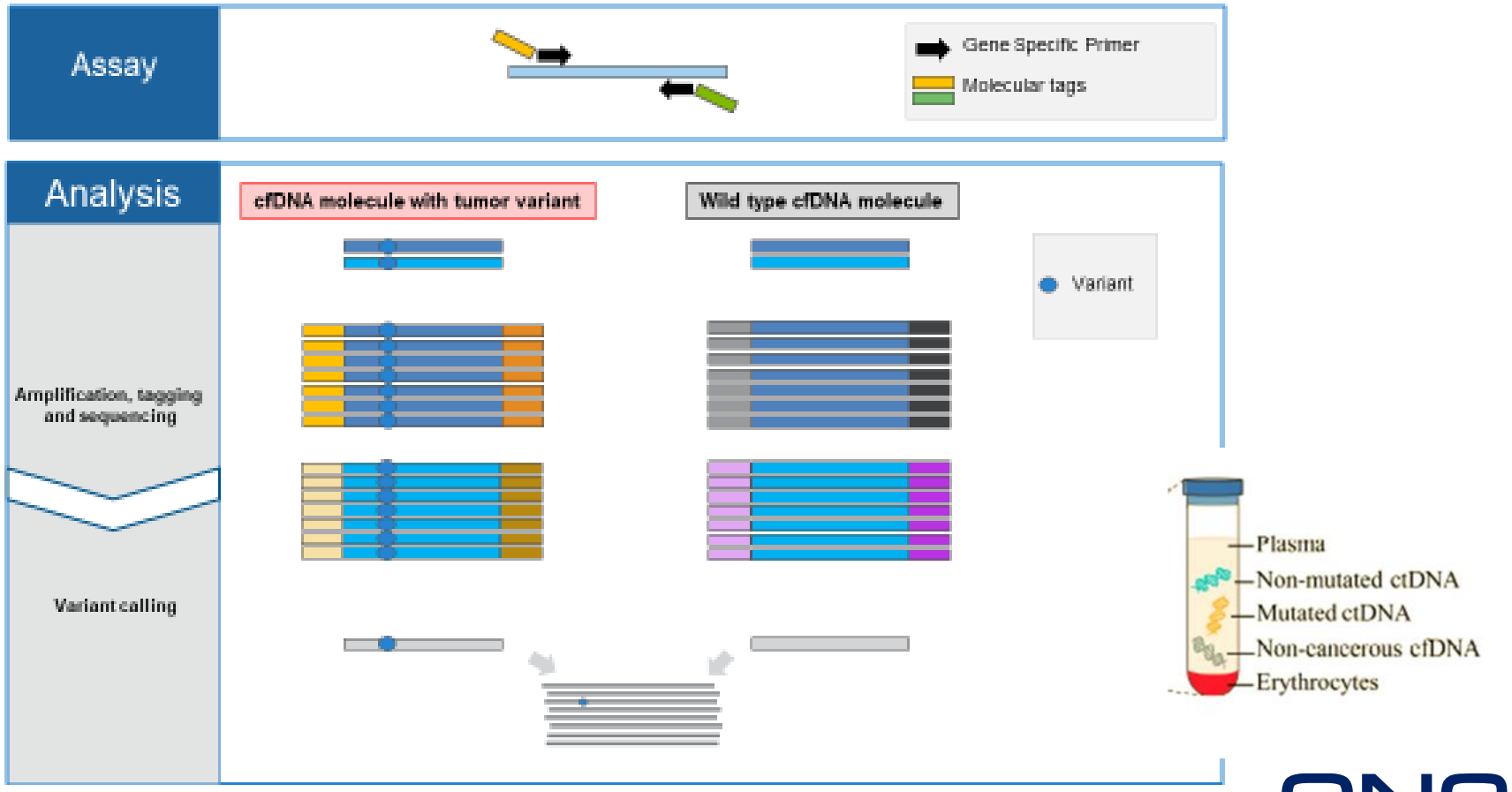
Unique Molecular Identifier (UMI)-Based Target Sequencing cf assay



Detection of somatic mutations at 0.1% frequency from cfDNA in peripheral blood with a multiplex next-generation sequencing assay Ion torrent, Thermo-fisher Poster

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Post sequencing analysis: Workflow overview

- STEP 1:Technical QC review on the entire run
- Per sample QC on Torrent browser suite
- Run research panel specific specific workflow and apply variant basic filter (analysis in Ion reporter)
- Selection of final variants to report (QC filtering in excel)
- Report generation

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Step 1: Technical run QC

- Chip loading > 80%
- Usable reads > in manufacturer specs.
- Polyclonality < 35%
- Low-quality < 15%
- Adapter Dimers < 5%
- Read-length Profile → Read trimming?
- Read-length profile – Bias? Trimming?
- Mean read length
- Degraded input material?
- Internal Control (TF) – Positive control for sequening reagents

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Step 2: Per sample coverage analysis assessment

Mapped reads	Minimum per panel
On target	>90%
Mapped reads	>1500x
Uniformity	>90%

- Check which amplicons are < defined threshold
- Are the drivers covered?

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Step 3: Variant calling in Ion Reporter
Step 4: Variant filtering in excel

- Run research panel specific workflow in IR
- Apply filter in IR
- Detailed filtering and variant selection in excel
- Confirm known problematic regions in IGV

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Step 3 and 4: which variants to report

Filter false positives and SNPs

- Exclude UCSC common SNPs
- Exclude synonymous mutations
- Exclude intronic mutations but look for those with splice sites (exclude p.? But not if close to exon-intron border, -4/+4 relevant)
- Exclude MAF and GMAF >0.01 and MAF ref+ and exclude benign and likely benign but always verify first
- Exclude homopolymers >5
- Exclude Phred <100
- Exclude coverage <500- consider tumour cell content
- Exclude strand bias >1/5
- Exclude VAF <5%
- Consideration to the type of sample- is it FFPE? Deamination artifacts C>T or G>A

Specific cell free variables to consider:

- Med read coverage: >25000
- Med molecular coverage: 2500
- Molecular count: >3 or previously confirmed >2
- 1.5 million reads
- Oncomine filter

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Interpretation and Reporting of Sequence Variants in Cancer

Analytic Interpretation: examining raw data and forming a conclusion about the quality or quantity of the analyte, ie. producing a reportable result.

Clinical research interpretation: describing what the result means regarding the blood sample'

The ins and outs of molecular pathology reporting

Véronique Tack[1] · Kelly Dufraing[1] · Zandra C. Deans[2] · Han J. van Krieken[3] · Elisabeth M. C. Dequeker[1]

Received: 25 January 2017 / Revised: 7 March 2017 / Accepted: 12 March 2017 / Published online: 26 March 2017

Laboratory Reports in Molecular Pathology - Gulley et al, Arch Pathol Lab Med—Vol 131, June 2007

The Journal of Molecular Diagnostics, Vol. 19, No. 3, May 2017

ELSEVIER

the Journal of Molecular Diagnostics
jmd.amjpathol.org

SPECIAL ARTICLE

Guidelines for Validation of Next-Generation Sequencing–Based Oncology Panels

A Joint Consensus Recommendation of the Association for Molecular Pathology and College of American Pathologists

Lawrence J. Jennings,*† Maria E. Arcila,*† Christopher Corless,*‡ Suzanne Kamel-Reid,*¶‖ Ira M. Lubin,*** John Pfeifer,*†† Robyn L. Temple-Smolkin,‡‡ Karl V. Voelkerding,*§¶¶ and Marina N. Nikiforova*‖‖

From the Next-Generation Sequencing Analytical Validation Working Group of the Clinical Practice Committee, Association for Molecular Pathology,‡‡ Bethesda, Maryland; the Ann & Robert H. Lurie Children's Hospital of Chicago,† Northwestern University's Feinberg School of Medicine, Chicago, Illinois; the Memorial Sloan Kettering Cancer Center,† New York, New York; the Department of Pathology and Knight Cancer Institute,‡ Oregon Health and Science University, Portland, Oregon; the Department of Clinical Laboratory Genetics,¶ University Health Network, Toronto, Ontario, Canada; the Department of Laboratory Medicine and Pathobiology,‖ the University of Toronto, Toronto, Ontario, Canada; the Centers for Disease Control and Prevention, ** Atlanta, Georgia; the Washington University School of Medicine,†† St. Louis, Missouri; ARUP Laboratories,§§ Salt Lake City, Utah; the Department of Pathology,¶¶ University of Utah, Salt Lake City, Utah; and the University of Pittsburgh Medical Center,‖‖ Pittsburgh, Pennsylvania

Accepted for publication January 24, 2017.

Address correspondence to Lawrence J. Jennings, M.D., Ph.D., Ann & Robert H. Lurie Children's Hospital of Chicago, 225 E Chicago Ave, Box 82, Chicago, IL 60611-2605. E-mail: ljennings@luriechildrens.org.

Next-generation sequencing (NGS) methods for cancer testing have been rapidly adopted by clinical laboratories. To establish analytical validation best practice guidelines for NGS gene panel testing of somatic variants, a working group was convened by the Association of Molecular Pathology with liaison representation from the College of American Pathologists. These joint consensus recommendations address NGS test development, optimization, and validation, including recommendations on panel content selection and rationale for optimization and familiarization phase conducted before test validation; utilization of reference cell lines and reference materials for evaluation of assay performance; determining of positive percentage agreement and positive predictive value for each variant type; and requirements for minimal depth of coverage and minimum number of samples that should be used to establish test performance characteristics. The recommendations emphasize the role of laboratory director in using an error-based approach that identifies potential sources of errors that may occur throughout the analytical process and addressing these potential errors through test design, method validation, or quality controls so that no harm comes to the patient. The recommendations

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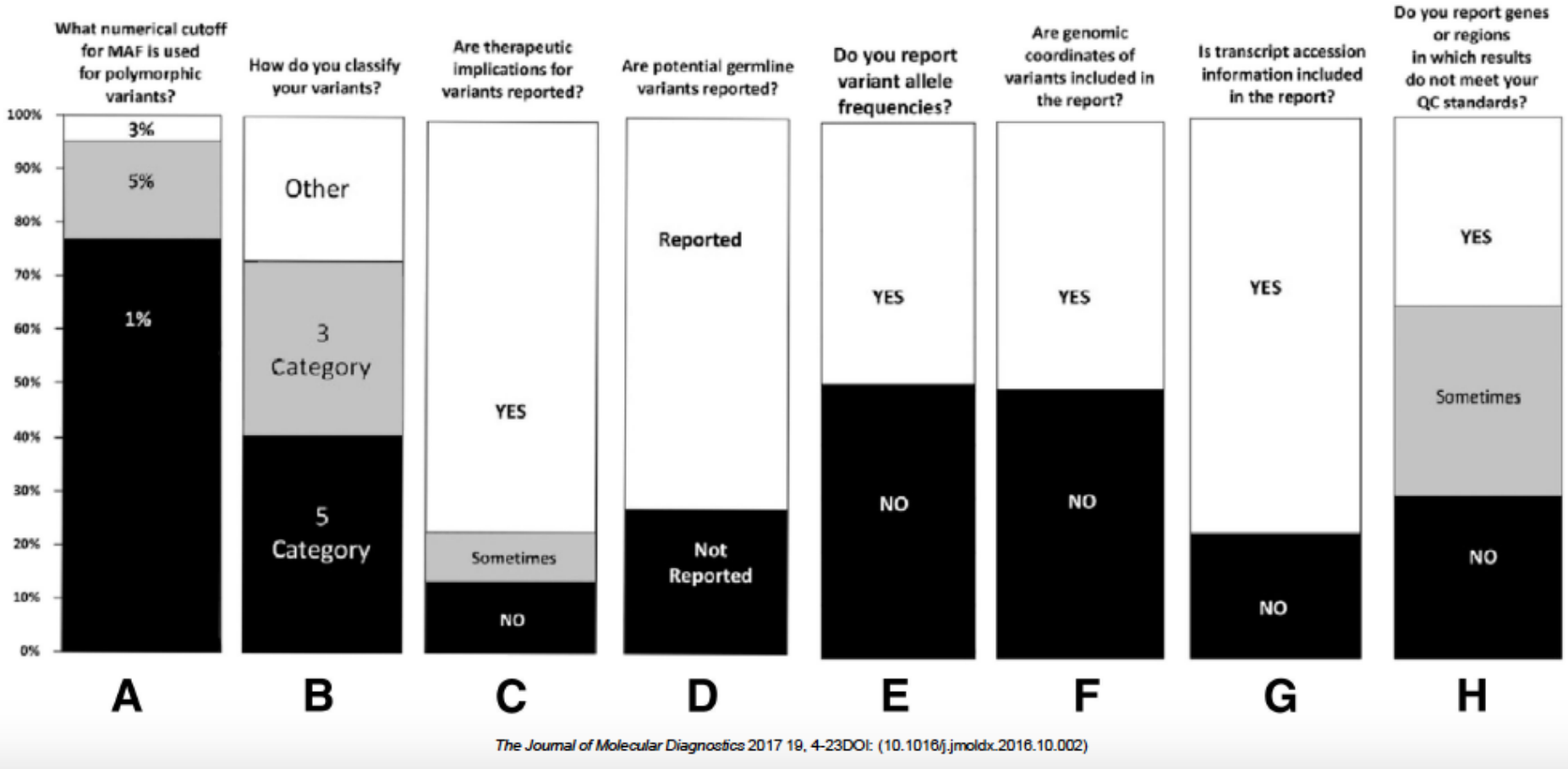
Guidelines for research molecular pathology reporting

Interpretation of Sequence Variants in Somatic Conditions AMP Working Group technical and reporting survey



The Journal of Molecular Diagnostics 2017 19, 4-23DOI: (10.1016/j.jmoldx.2016.10.002)

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Example of Oncomine™ Reporter Case

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
KRAS	p.(G12D)	c.35G>A	p.G12D	chr12:25398284	1.01%	NM_033360.3	missense
TP53	p.(R175H)	c.524G>A	p.R175H	chr17:7578406	1.12%	NM_000546.5	missense

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2 Clinically Significant Biomarkers
0 Therapies Available
44 Clinical Trials

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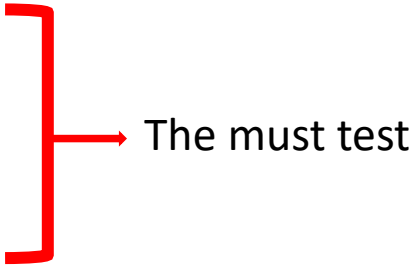
Cell-free Lung research assays

ALK[F]
BRAF
EGFR
ROS1[F]
ERBB2
KRAS
MAP2K1
MET[C]
NRAS
PIK3CA
RET[F]
TP53



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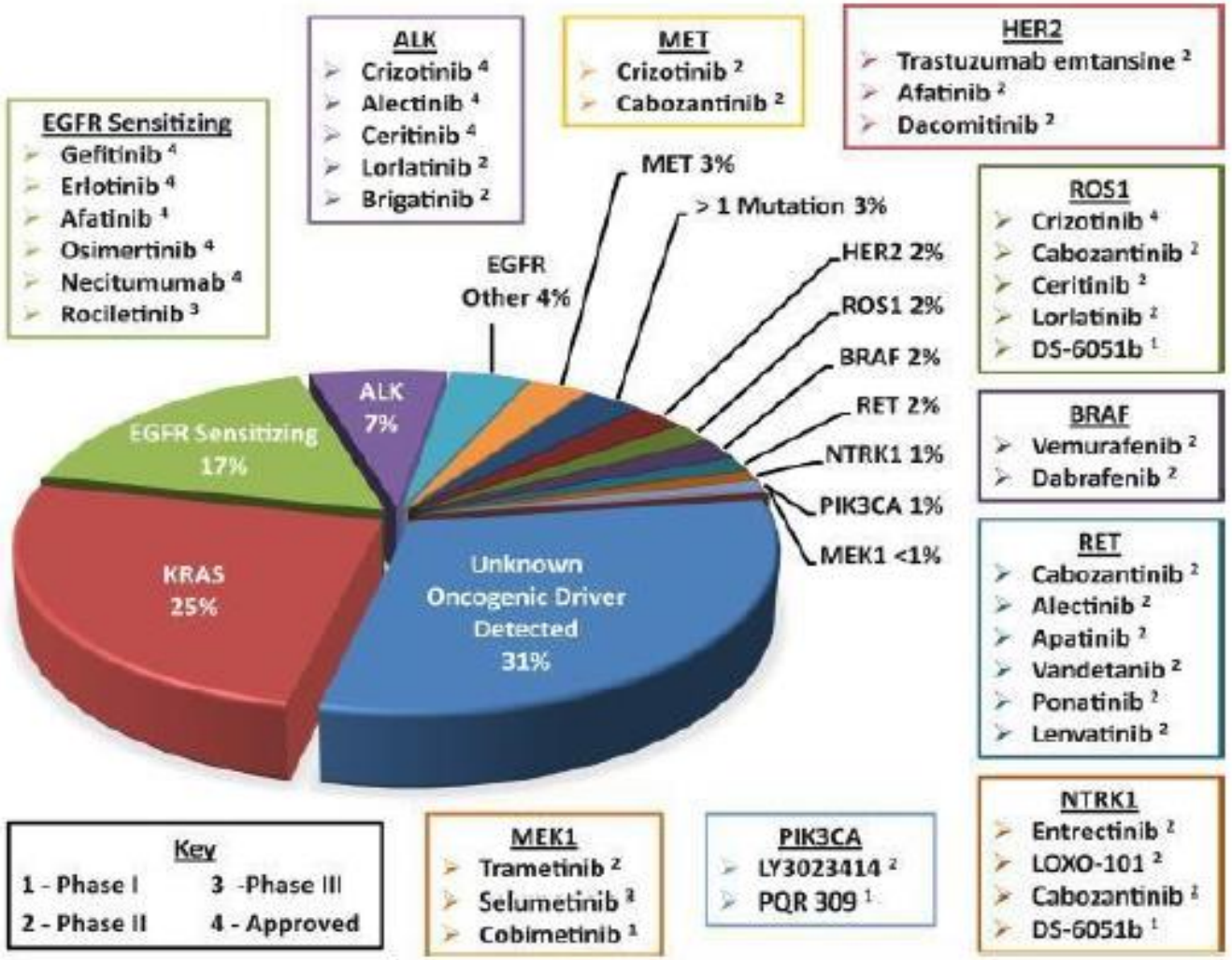
Research of predictive biomarker testing in NSCLC



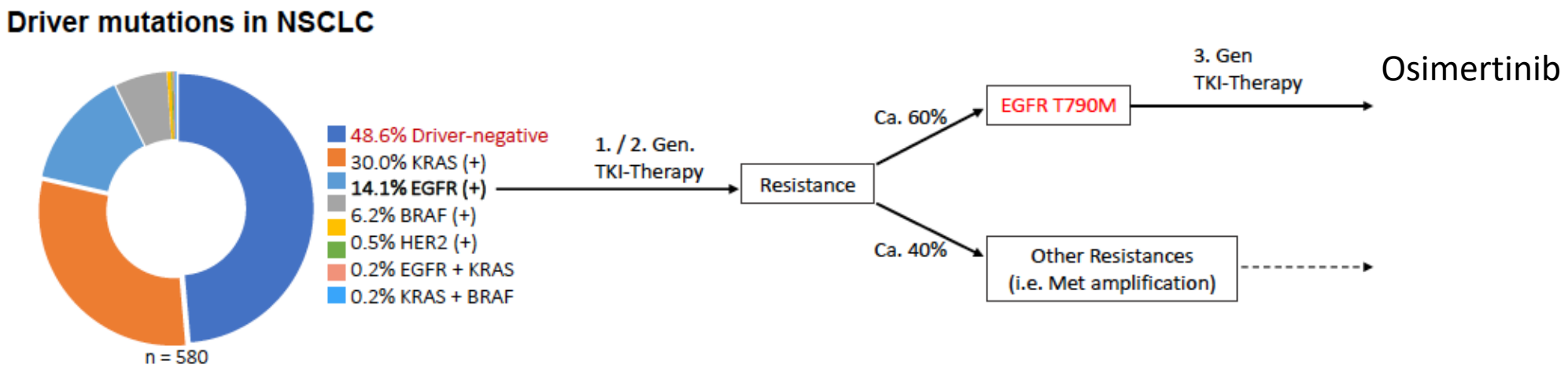
- **Mutations**
- **Rearrangements**
- **Amplifications**

Research exploring the utility in future targeted therapy

Tsao AS et al., JTO 2016

Applications for Liquid Biopsy

Detection of T790M resistance mutation in NSCLC



Diaz LA Jr, Bardelli A: Liquid biopsies: Genotyping circulating tumor DNA. J Clin Oncol 32:579-586, 2014.

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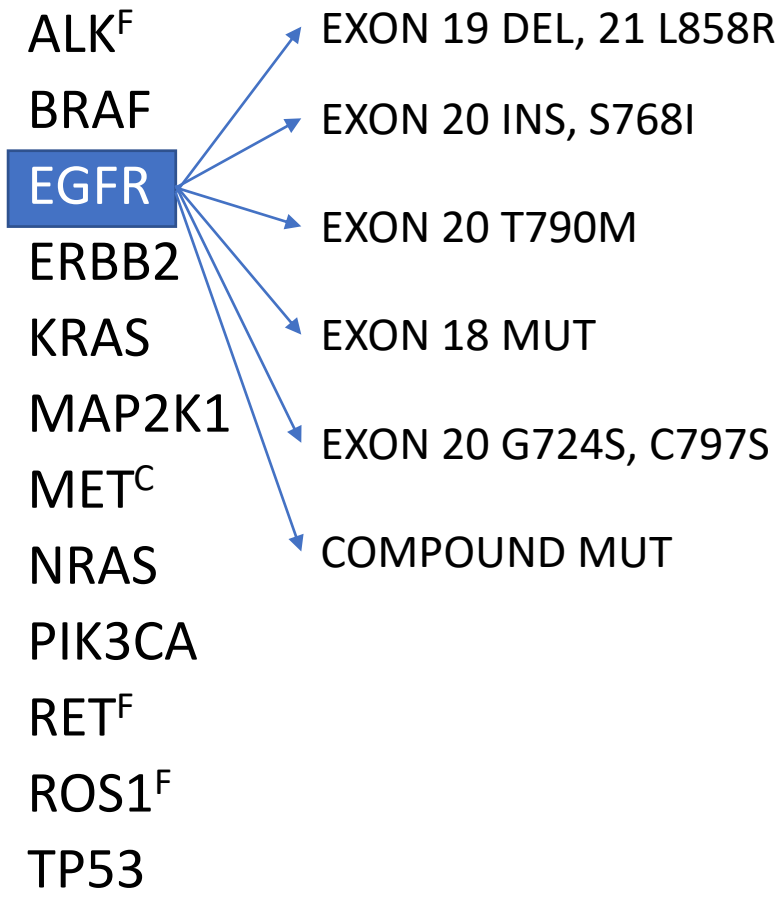
Oncomine™ Lung cfTNA Research Assay



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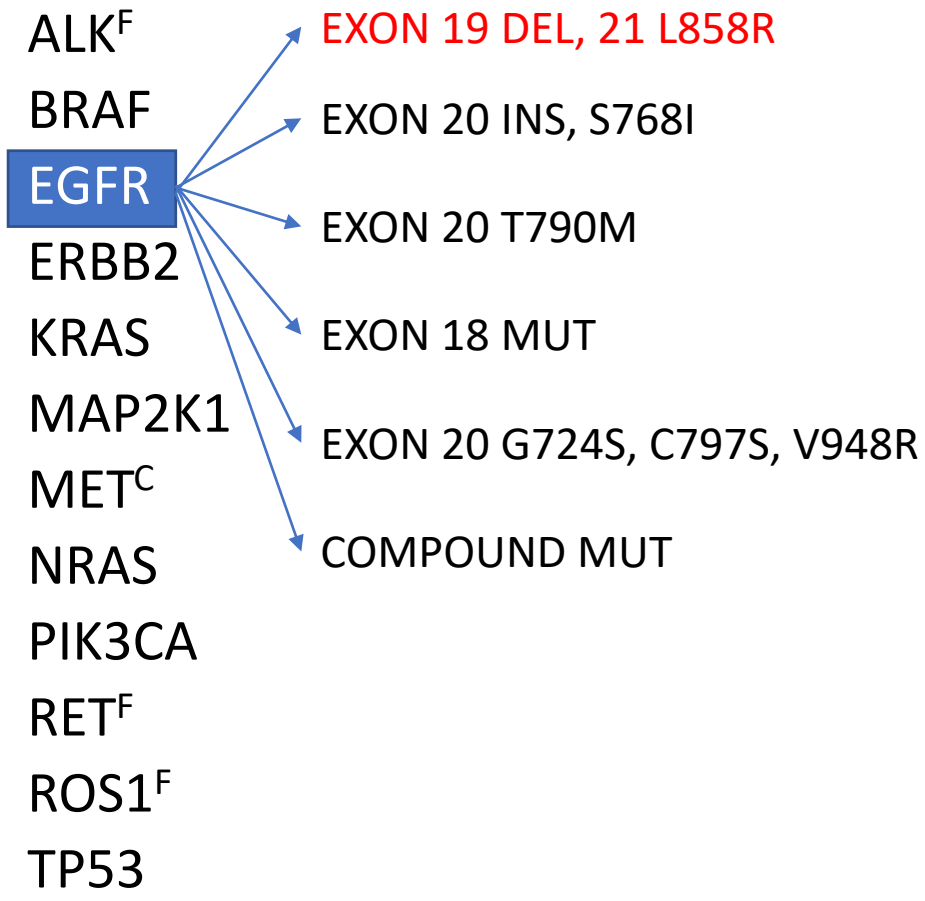
Research studies highlighting potential application of cfNA testing in Oncology research



Different subtypes of EGFR exon19 mutation can affect prognosis of patients with non-small cell lung adenocarcinoma

Yingying Tian[1,2], Jiuzhou Zhao[1], Pengfei Ren[1], Bo Wang[1], Chengzhi Zhao[1], Chao Shi[1], Bing Wei[1], Jie Ma[1], Yongjun Guo[1]*

1 Department of Molecular Pathology, Henan Cancer Hospital, The Affiliated Cancer Hospital, Zhengzhou University, Zhengzhou, China, **2** School of Pharmaceutical Sciences, Zhengzhou University, Zhengzhou, China

PLoS ONE 2018

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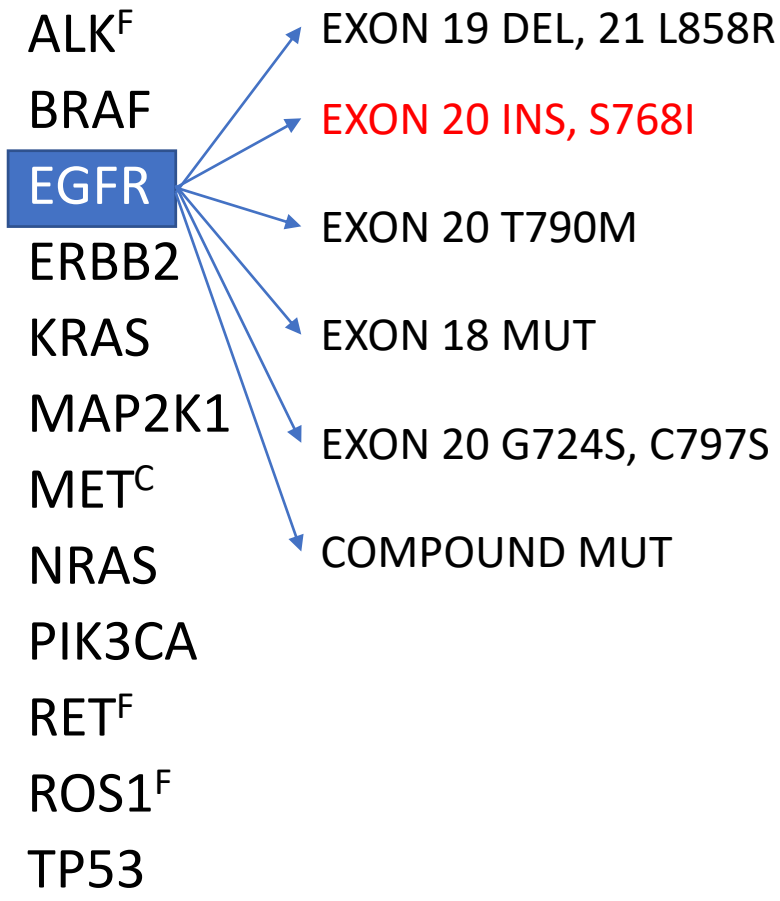
Research studies highlighting potential application of cfNA testing in Oncology research



Targeting *EGFR* exon 20 insertion mutations in non-small cell lung cancer

Simon Vyse[1] and Paul H. Huang[1]

Signal transduction and targeted therapy 2019

Effectiveness of afatinib after ineffectiveness of gefitinib in an advanced lung adenocarcinoma patient with a single EGFR exon 20 S768I mutation: a case report

OncoTargets and Therapy 2018

Osimertinib Did Not Respond to a Pulmonary Adenocarcinoma with Triple Mutations of Epidermal Growth Factor Receptor, G719S, T790M and S768I

Seigo Minami Shouichi Ihara Tsunehiro Tanaka Hideyasu Okada Kazuki Hashimoto Kiyoshi Komuta

Case Rep Oncology 2019

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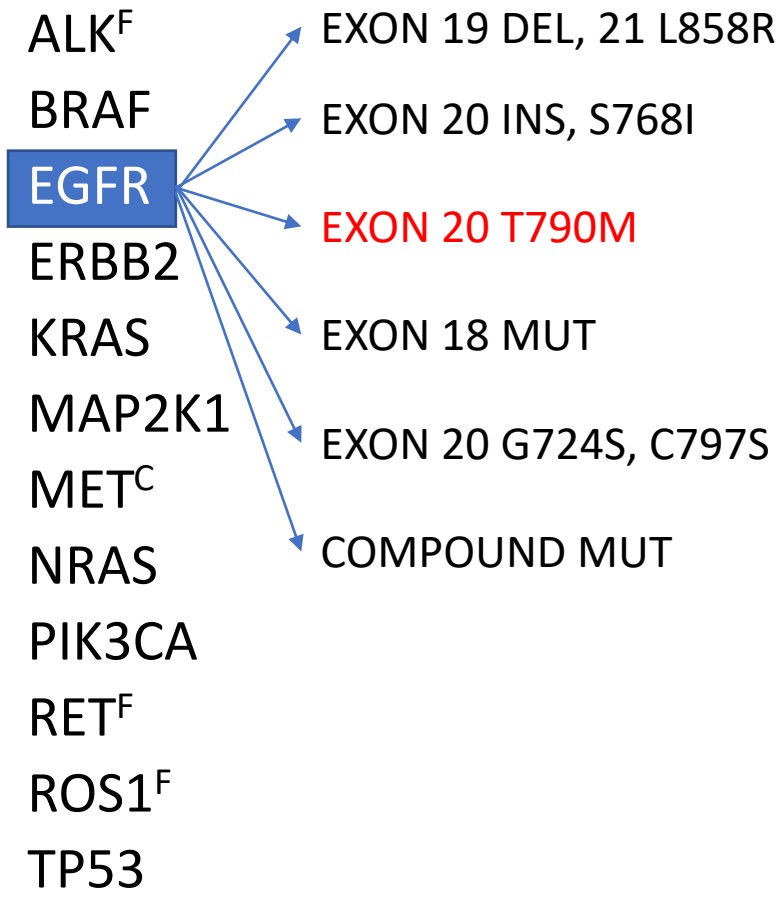
Research studies highlighting potential application of cfNA testing in Oncology research



Liquid-Biopsy-Based Identification of *EGFR* T790M Mutation-Mediated Resistance to Afatinib Treatment in Patients with Advanced *EGFR* Mutation-Positive NSCLC, and Subsequent Response to Osimertinib

Maximilian J. Hochmair[1] · Anna Buder[2] · Sophia Schwab[1] · Otto C. Burghuber[1,3] · Helmut Prosch[4] · Wolfgang Hilbe[5] · Agnieszka Cseh[6] · Richard Fritz[6] · Martin Filipits[2]

Targeted Oncology 2019

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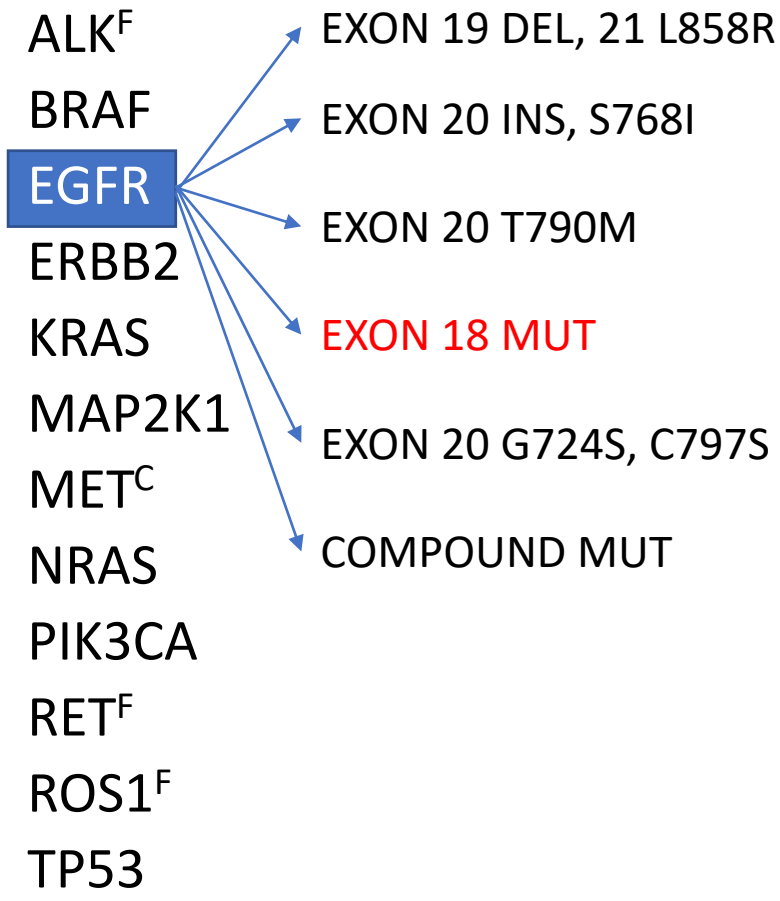
Research studies highlighting potential application of cfNA testing in Oncology research



EGFR Exon 18 Mutations in Lung Cancer: Molecular Predictors of Augmented Sensitivity to Afatinib or Neratinib as Compared with First- or Third-Generation TKIs

Yoshihisa Kobayashi[1], Yosuke Togashi[2], Yasushi Yatabe[3], Hiroshi Mizuuchi[1,4], Park Jangchul[5,6], Chiaki Kondo[3], Masaki Shimoji[1], Katsuaki Sato[1], Kenichi Suda[1], Kenji Tomizawa[1], Toshiki Takemoto[1], Toyoaki Hida[5], Kazuto Nishio[2], and Tetsuya Mitsudomi[1]

Clin Cancer Res 2015

Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon *EGFR* mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6

Prof James C-H Yang MD [a, †], Lecia V Sequist MD [b, †], Sarayut Lucien Geater MD [c], Prof Chun-Ming Tsai MD [d], Prof Tony Shu Kam Mok MD [e], Prof Martin Schuler MD [f], Prof Nobuyuki Yamamoto MD [g], Prof Chong-Jen Yu MD [h], Sai-Hong I Ou MD [i], Prof Caicun Zhou MD [j], Daniel Massey MSc [l], Victoria Zazulina MD [k], Prof Yi-Long Wu MD [m]

Lancet Oncology 2015

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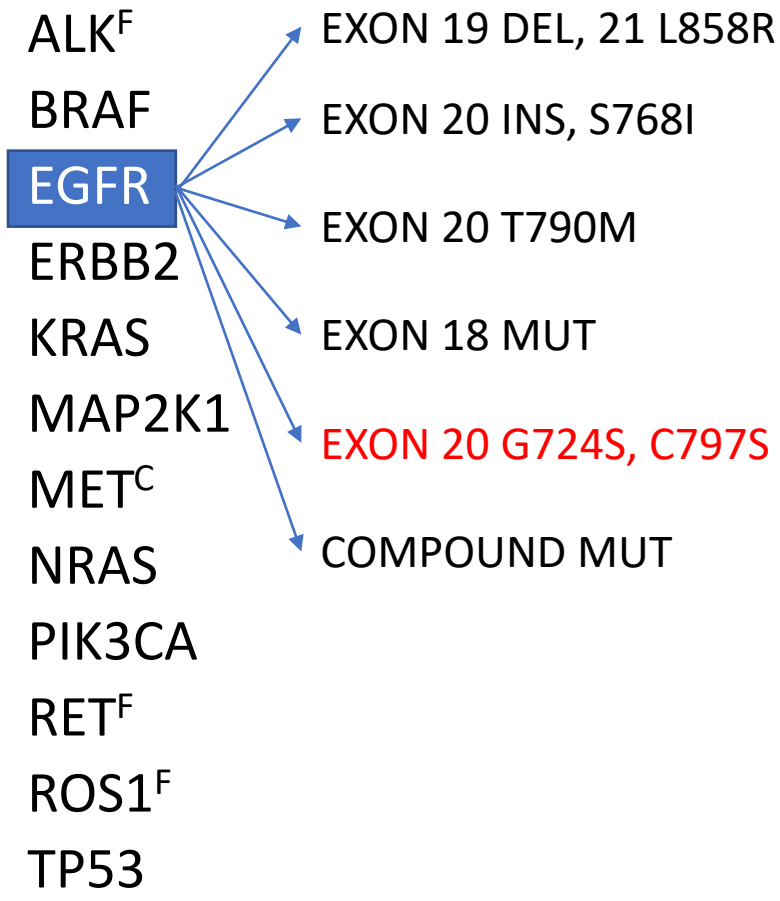

On-target Resistance to the Mutant-Selective EGFR Inhibitor Osimertinib Can Develop in an Allele-Specific Manner Dependent on the Original EGFR-Activating Mutation

Benjamin P. Brown[1,2], Yun-Kai Zhang[3], David Westover[3], Yingjun Yan[3], Huan Qiao[3], Vincent Huang[3], Zhenfang Du[3], Jarrod A. Smith[2,4], Jeffrey S. Ross[5], Vincent A. Miller[5], Siraj Ali[5], Lyudmila Bazhenova[6], Alexa B. Schrock[5], Jens Meiler[1,2,7], and Christine M. Lovly[3,7]

Clin Cancer Res 2019

***EGFR* C797S mutation mediates resistance to third-generation inhibitors in T790M-positive non-small cell lung cancer**

Shuhang Wang[1], Stella T. Tsui[2], Christina Liu[3], Yongping Song[4] and Delong Liu[4*]

J Hematol Oncol 2016

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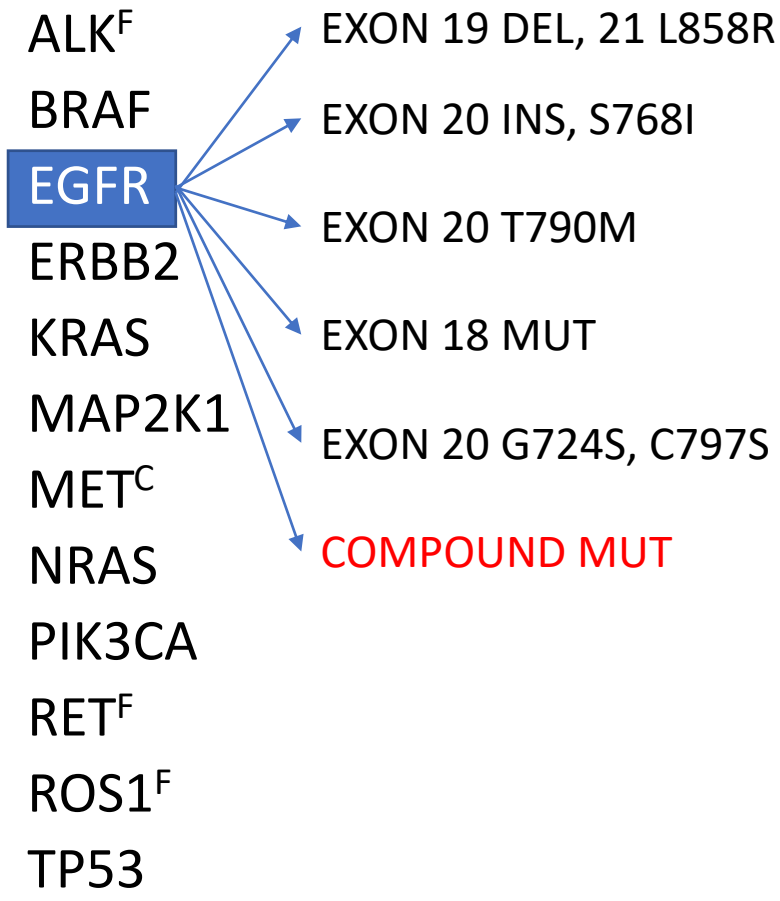

Outcome of uncommon EGFR mutation positive newly diagnosed advanced non-small cell lung cancer patients: a single center retrospective analysis

Lung Cancer Targets Therapy 2019

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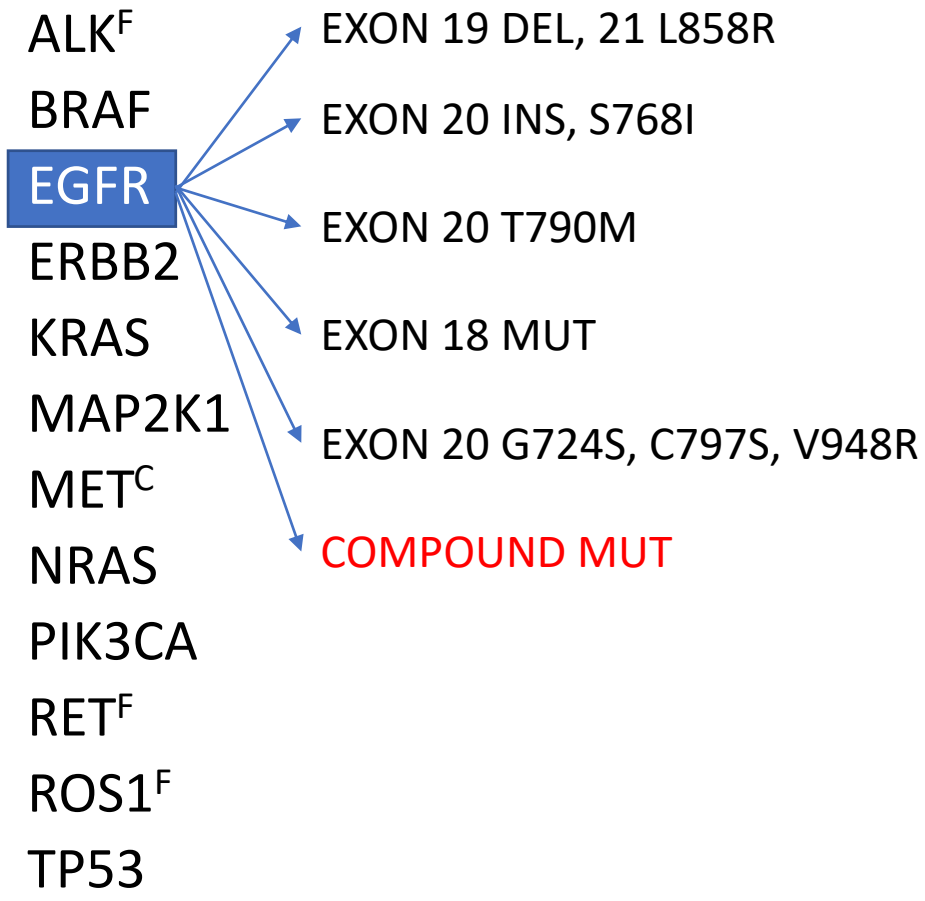

Uncommon EGFR mutation types	N=83	%
Uncommon EGFR single mutations		
Exon 18 G719X	8	9.6
Exon 20 insertion	15	19.3
Exon T790M	10	12.0
Exon 20 768I	3	3.6
Exon 21 L861Q	3	3.6
Complex dual mutation positivity	43	50.6
Exon 19 deletion + exon 20 T790M	17	20.4
Exon 21 L858R + exon 20 T790M	15	18.0
Exon 18 G719X + exon 20768I	03	3.6
Exon 20 S768I + exon 21 L858R	02	2.4
Exon 18 G719X + exon 20 T790M	01	1.2
Exon 18 G719X + exon 21 L858R	01	1.2
Exon 20 insertion + exon 19 deletion	01	1.2
Exon 21 L858R + L861Q	01	1.2
Exon 20 T790M + exon 20 S768I	01	1.2
Exon 21 L861I + exon 20 T790M	01	1.2
Complex triple mutation Positivity (exon 18 G719X + exon 20 S768I + exon 21 L858R)	1	1.2
Uncommon mutation frequency as per predicted TKI sensitivity		
TKI sensitive single mutations (G719X, S768I, and L861Q)	14	16.8
TKI insensitive single mutations (exon 20 insertion/T790M)	25	30.1
TKI sensitive dual mutations	4	4.8
TKI sensitive/insensitive complex mutations	40	48.2

Lung Cancer Targets Therapy 2019

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BRAF
EGFR
ERBB2
KRAS
MAP2K1
MET[C]
NRAS
PIK3CA
RET[F]
ROS1[F]
TP53

KRAS oncogene in non-small cell lung cancer: clinical perspectives on the treatment of an old target

Marta Román[1,2], Iosune Baraibar[1,2], Inés López[2], Ernest Nadal[3], Christian Rolfo[4], Silvestre Vicent[2,5,6] and Ignacio Gil-Bazo[1,2,5,6*]

Molecular Cancer 2018

Characteristics of Lung Cancers Harboring *NRAS* Mutations

Kadoaki Ohashi, Lecia V. Sequist, Maria E. Arcila, Christine M. Lovly, Xi Chen, Charles M. Rudin, Teresa Moran, David Ross Camidge, Cindy L. Vnencak-Jones, Lynne Berry, Yumei Pan, Hidefumi Sasaki, Jeffrey A. Engelman, Edward B. Garon, Steven M. Dubinett, Wilbur A. Franklin, Gregory J. Riely, Martin L. Sos, Mark G. Kris, Dora Dias-Santagata, Marc Ladanyi, Paul A. Bunn Jr, and William Pao

Clin Cancer Res 2013

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ROS1[F]

TP53

BRAF inhibitors in metastatic non-small cell lung cancer

Geòrgia Anguera, Margarita Majem

MAP2K1 (*MEK1*) Mutations Define a Distinct Subset of Lung Adenocarcinoma Associated with Smoking

Maria E. Arcila, Alexander Drilon, Brooke E. Sylvester, Christine M. Lovly, Laetitia Borsu, Boris Reva, Mark G. Kris, David B. Solit, and Marc Ladanyi

Clin Cancer Res 2015

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TP53

The Role of *PIK3CA* Mutations among Lung Adenocarcinoma Patients with Primary and Acquired Resistance to EGFR Tyrosine Kinase Inhibition

Nature Scientific Reports 2016

Shang-Gin Wu[1,2], Yih-Leong Chang[3], Chong-Jen Yu[2,4], Pan-Chyr Yang[2,4] & Jin-Yuan Shih[2,4]

Prognostic value of *KRAS/TP53/PIK3CA* in non-small cell lung cancer

Oncology Letters 2018

JIAYI ZHAO[1*], YIPING HAN[1*], JIAMEI LI[2*], RONG CHAI[1*] and CHONG BAI[1]

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Research studies highlighting potential application of cfNA testing in Oncology research

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TP53

Targeted Treatments Emerge for HER2 Mutations in Lung Cancer

Lalitha Priya Chandrashekhar
Published Online: Sep 20,2018

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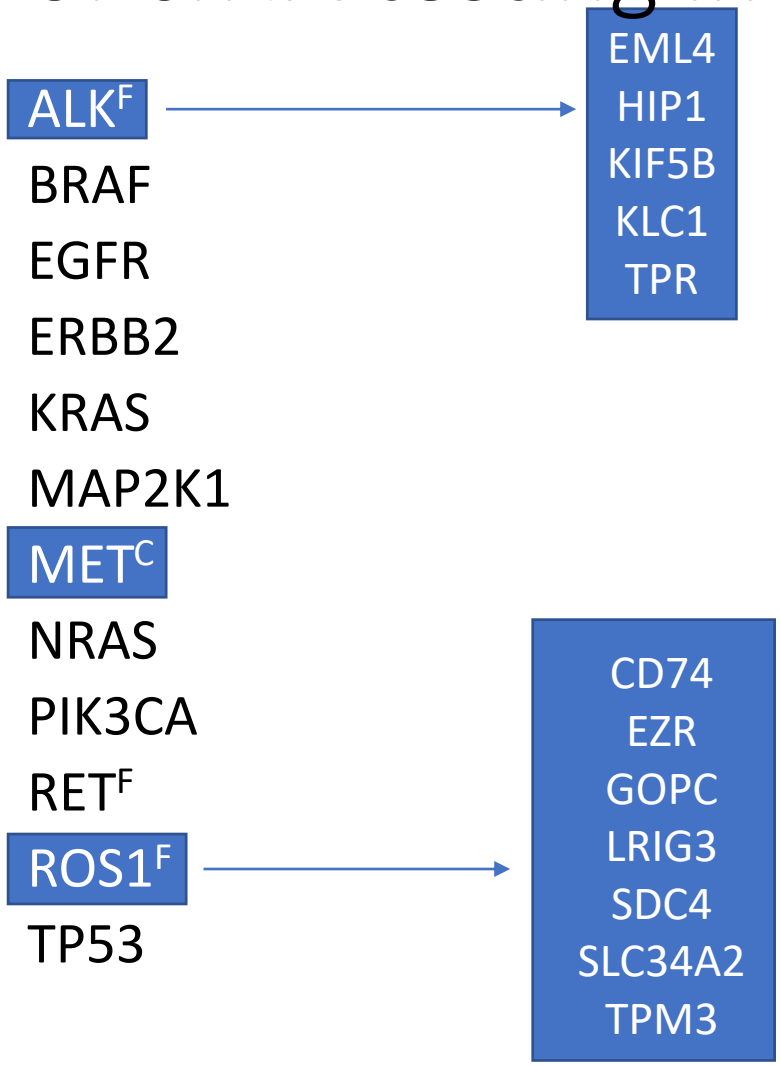

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- ALK[F]
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- MET[C]
- NRAS
- PIK3CA
- RET[F]
- ROS1[F]
- TP53

MET Inhibition in Non-Small Cell Lung Cancer

Rehman S, Dy GK. EMJ Respir 2018

ROS1 mutation non-small cell lung cancer—access to optimal treatment and outcomes

Amit Joshi[1], Nikhil Pande[1], Vanita Noronha[1], Vijay Patil[1], Rajiv Kumar[2], Anuradha Chougule[1], Vaishakhi Trivedi[1], Amit Janu[3], Abhishek Mahajan[3] and Kumar Prabhash[1]

ecancer 2019

TKI-resistant *ALK*-rearranged lung adenocarcinoma with secondary CTNNB1 p.S45V and tertiary ALK p.I171N mutations

Lung Cancer: Targets and Therapy 2019

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MET[C]
NRAS
PIK3CA
RET[F]
ROS1[F]
TP53

Targeting RET-rearranged non-small-cell lung cancer: future prospects

Bronte G et al. Lung Cancer: Targets and Therapy 2019

RET fusion in advanced non-small-cell lung cancer and response to cabozantinib

A case report

Yucong Wang, MB[a], Yinghui Xu, MD[a], Xu Wang, MD[a], Chao Sun, MM[a], Ye Guo, MM[a], Guoguang Shao, MD[b], Zhiguang Yang, MD[b], Shi Qiu, MM[a], Kewei Ma, MD[a,*]

Medicine 2019

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