



Clinical Evidence for Genomic Medicine Sustainability: State of Science and Gaps – Molecular Profiling in Cancer

August 30, 2016

Roger D. Klein, MD JD

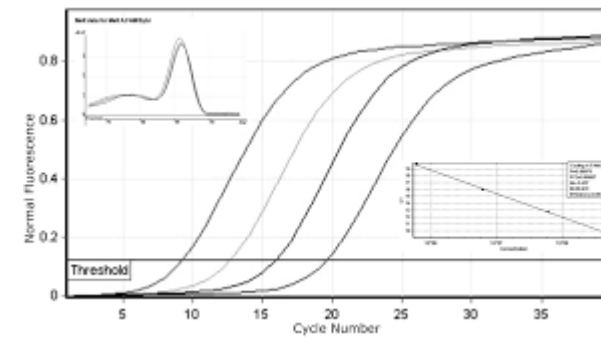
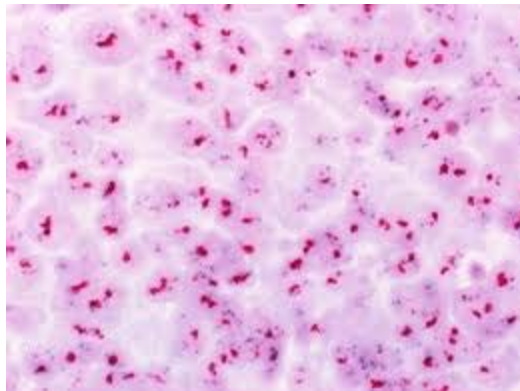
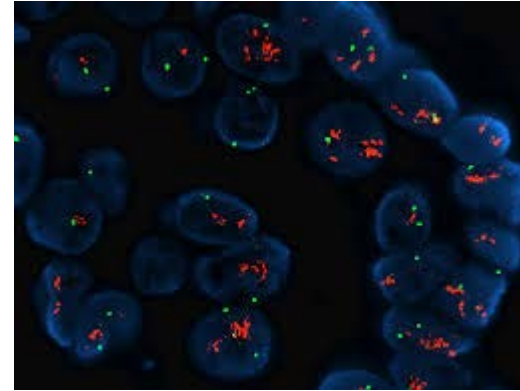
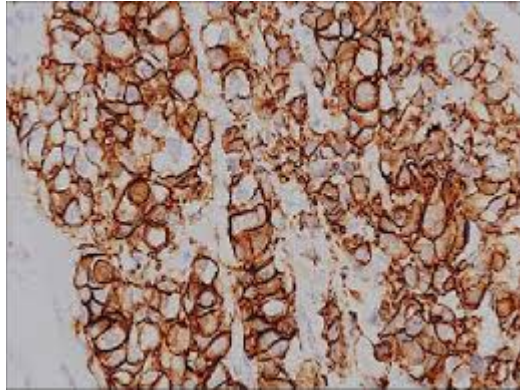
Medical Director, Molecular Pathology

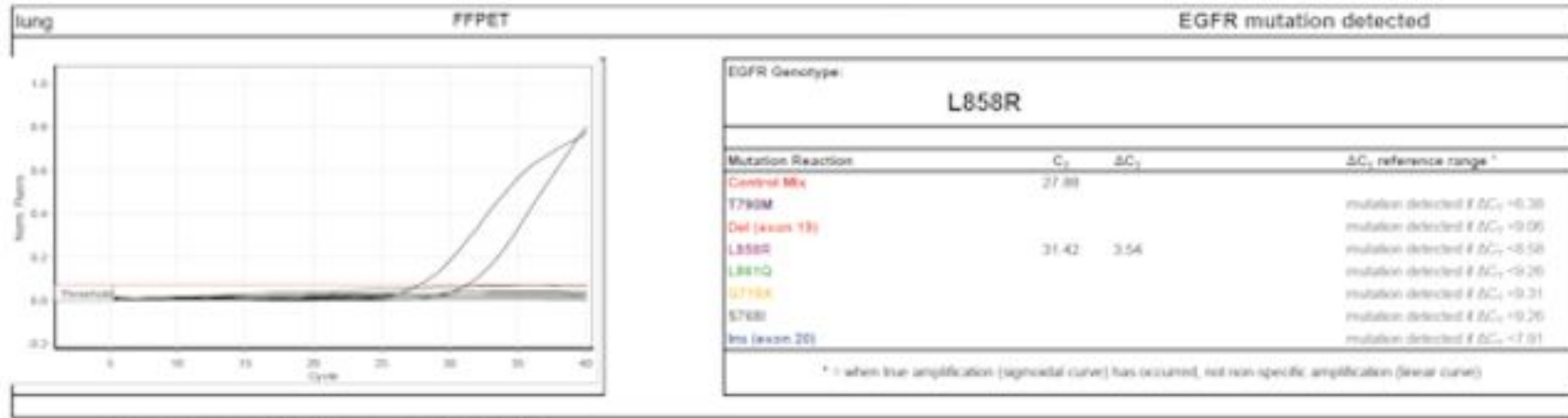


Traditional Analysis

- Tumor type and marker specific
- IHC, ISH, PCR
- Single or small number of markers
- Highly specific, limited information

HER2 (ERBB2)



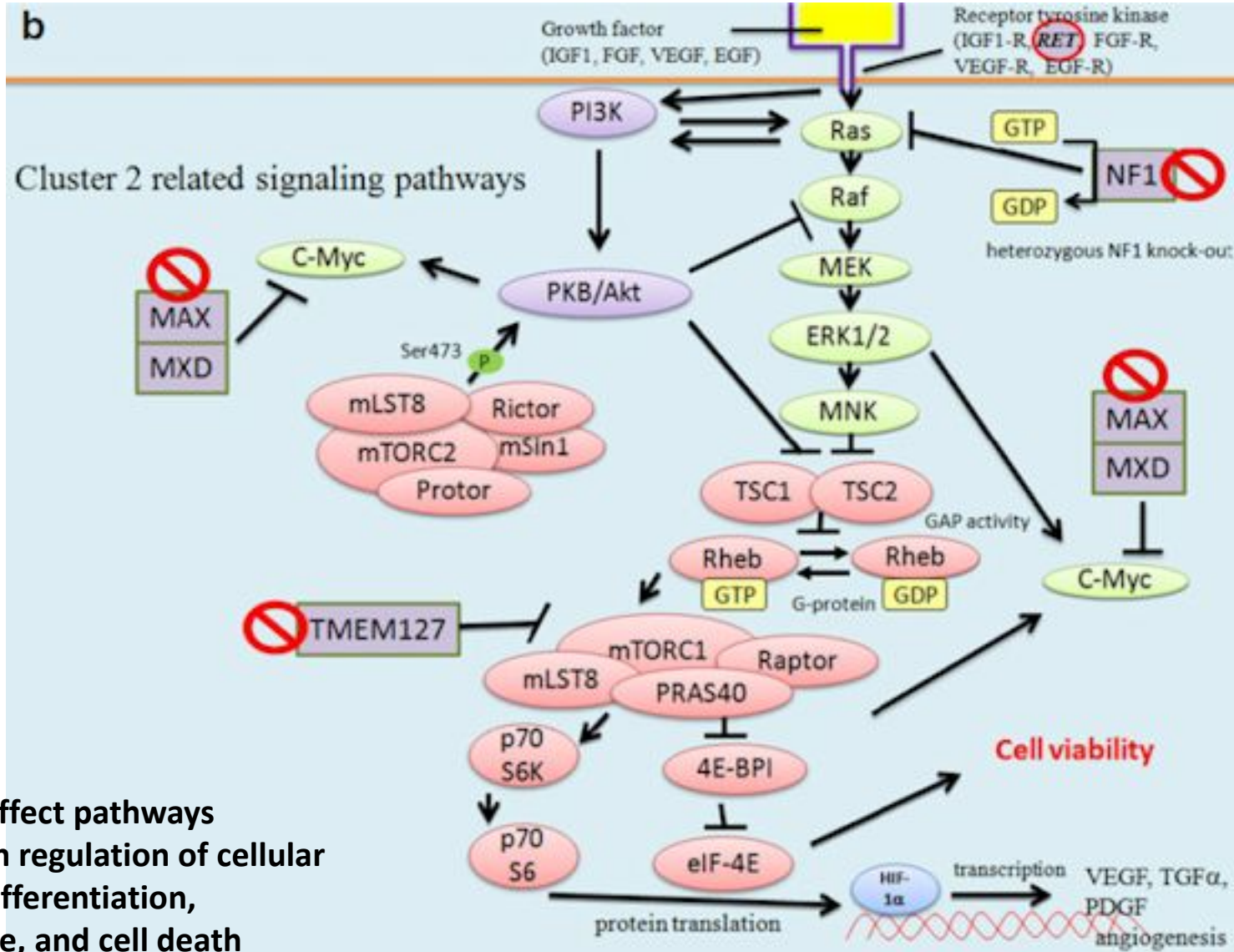


Comments: The specimen submitted for analysis contained 37% tumor cells

The recurrent mutation arising as a result of the leucine to arginine amino acid substitution at position 858 within exon 21 of the EGFR gene, which encodes part of the tyrosine kinase domain, results in increased receptor activation after ligand binding. Patients harboring these mutations have increased sensitivity to TKIs over patients with wild type EGFR. Analysis of the crystal structures of L858R EGFR mutants has demonstrated that the kinase is activated through disruption of autoinhibitory interactions, resulting in receptors with 10-fold more activity compared to wild type EGFR receptors. (reference: 1)



PRESENTED BY: Roger D. Klein, MD JD, Cleveland Clinic



Changes affect pathways involved in regulation of cellular growth, differentiation, senescence, and cell death (apoptosis)

Next Generation Sequencing



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How to Read the FoundationOne[™] Report

THE FIRST PAGE OF THE REPORT SHOWS

the patient and ordering physicians information...

The genomic alterations identified in the hundreds of genes assayed...

The targeted therapies that may be relevant based on those genomic alterations both in the patients tumor type and in other tumor types...

and whether there are relevant clinical trials.



Genomic Alterations Detected	FDA Approved Therapies (in patient's tumor type)	FDA Approved Therapies (in another tumor type)	Potential Clinical Trials
EGFR N771_P772>KFP	Erlotinib Gefitinib	Cetuximab Panitumumab	Yes, see clinical trials section
CCND1 amplification	None	None	Yes, see clinical trials section
ARID1A Q633*	None	None	None





iontorrent

Ion AmpliSeq Cancer Hotspot Panel v2

Just one tube. Just 10ng of DNA. Just one day.

The Ion AmpliSeq™ Cancer Hotspot Panel v2 allows translational and disease researchers to fast-track oncology research by surveying hotspot regions of 50 oncogenes and tumor suppressor genes, with wide coverage of the *KRAS*, *BRAF* and *EGFR* genes.

This research panel, with improved primer design, contains 207 primer pairs in a single tube and requires as little as 10ng of DNA, enabling researchers to sequence challenging samples such as formalin-fixed, paraffin-embedded (FFPE) tissue. The convenient predesigned panel allows researchers to focus on data generation and analysis, not on the labor-intensive primer design and target selection steps. While hybridization-based target selection methods require 7 to 72 hours to complete both target selection and library preparation, Ion AmpliSeq™ technology makes it possible to complete the entire process in about 3.5 hours using simple PCR reactions. Additionally, Ion AmpliSeq™ library construction steps are automated using standard 96-well plate-based protocols, further simplifying the workflow and allowing large projects to be rapidly completed without additional sample transfer steps.

"Sequencing gene panels with Ion Torrent™ technology is complete. You have the Ion AmpliSeq™ gene selection technology, the Ion PGM™ sequencing system and also the Ion Reporter™ analysis software.

For me, it is important to have a whole integrated solution, so researchers can advance from the tumor to results."

Pierre Laurent-Puig, M.D., Ph.D.
Paris-Descartes University
Medical School, Paris, France

NGS in Oncology Practice

- Diagnosis
 - help identify tumor vs. benign
 - tumor subtypes
- Appropriate targeted therapy
- Identification of resistance mutations
 - primary
 - secondary
- **Off-label use and clinical trial selection**

Use of NGS in cancer

- Use of NGS in has resulted in discovery of large numbers of mutations with potential prognostic and therapeutic relevance
 - many genes overlap different cancer types
 - germline variants must be distinguished
- Translation into useful clinical test requires ability to
 - accurately and reproducibly detect variations
 - **meaningfully interpret results**
 - **effectively communicate results**

Questions in Interpretation

- Is the mutated gene potentially relevant to the patient's management?
 - if so, in what way?
- Is the particular variant potentially relevant to the patient's management?
 - If so in what way?
- Is it of the type that appears to respond to therapy, impact prognosis, or aid in diagnosis?

MOLECULAR PROFILING TO GUIDE CANCER TREATMENT

Policy Number: 2016T0576C

Effective Date: July 1, 2016

COVERAGE RATIONALE

Molecular profiling using multiplex or next generation sequencing (NGS) technology is proven and medically necessary for guiding systemic chemotherapy in patients with metastatic stage IV non-small cell lung cancer (NSCLC) when the following criteria are met:

- Molecular profiling using multiplex or NGS technology to test for epidermal growth factor receptor (*EGFR*) mutations, human epidermal growth factor receptor 2 (*HER2*) mutations, *RET* rearrangements, and anaplastic lymphoma kinase (*ALK*) gene arrangements.

Molecular Profiling to Guide Cancer Treatment
UnitedHealthcare Commercial Medical Policy

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Effective 07/01/2016

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- **Note:** See the National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline for Non-Small Cell Lung Cancer, available at: www.nccn.org, for updates regarding oncogenes used in molecular profile testing for NSCLC. (Accessed April 21, 2016)
- The laboratory providing molecular profiling testing services must be approved by the New York State Department of Health for performing the molecular profile test.
 - **Note:** See the following website for clinical laboratories holding a New York State Department of Health permit in the category of oncology molecular and cellular tumor markers: <http://www.wadsworth.org/labcert/clep/CategoryPermitLinks/CategoryListing.htm>. (Accessed April 21, 2016)

Molecular profiling using multiplex or NGS technology is unproven and not medically necessary for ALL other indications.

There is insufficient evidence in the clinical literature demonstrating that molecular profiling has a role in clinical decision-making or has a beneficial effect on health outcomes for other indications. Further studies are needed to determine the analytic validity, clinical validity and/or clinical utility of molecular profiling using multiplex or NGS technology for other indications.

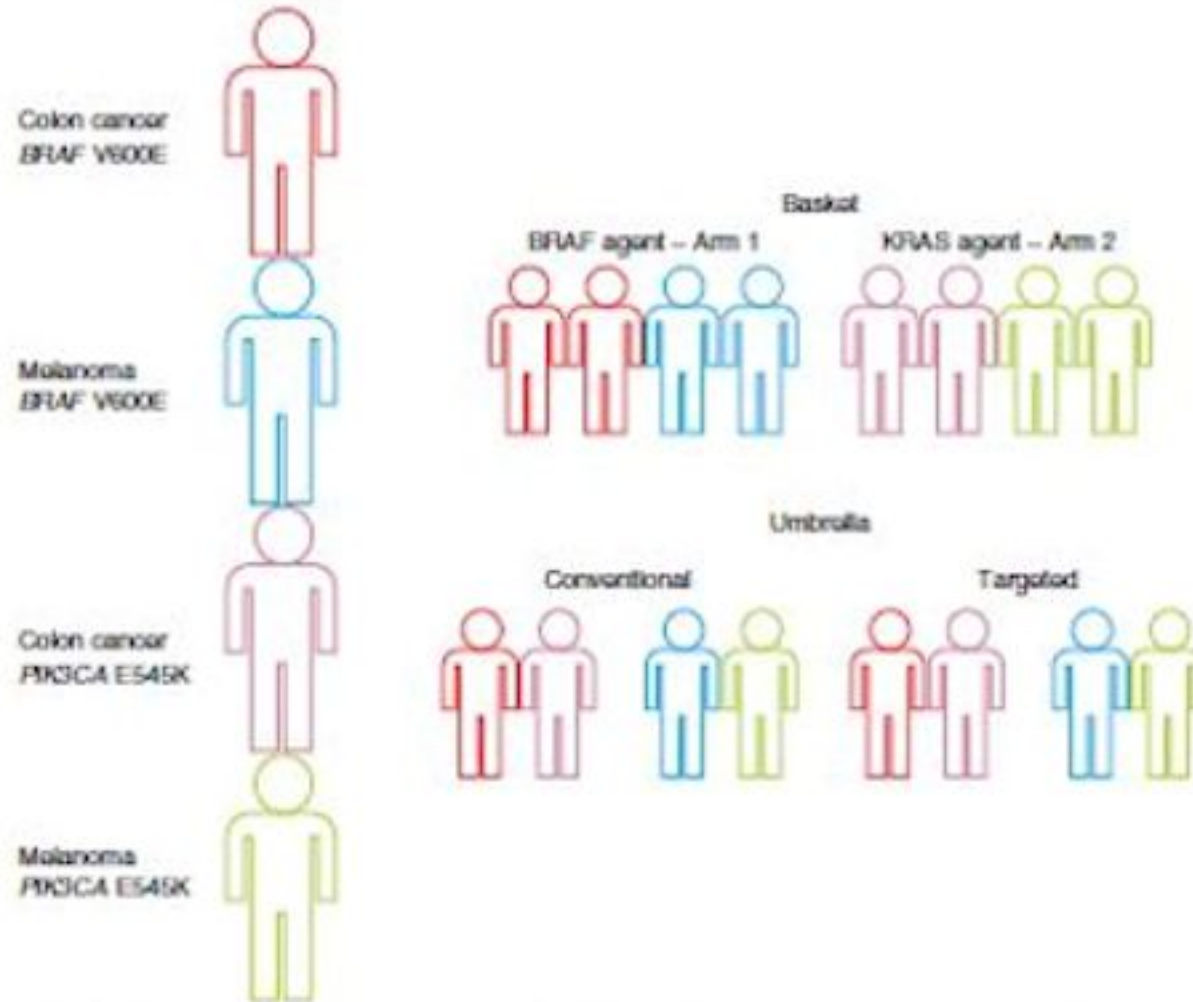


Fig. 4 An illustration of new clinical trial designs. Basket and umbrella trials both incorporate genomic data into the basic construction of the trial. Basket trials are designed around specific mutations, regardless of the primary tumor site. Umbrella trials are first separated by primary tumor site and then split into conventional therapy and precision medicine arms

PRESS RELEASES

NCI Press Release

NCI launches trial to assess the utility of genetic sequencing to improve patient outcomes

Posted: January 30, 2014

A pilot trial to assess whether assigning treatment based on specific gene mutations can provide benefit to patients with metastatic solid tumors is being launched this month by the National Cancer Institute (NCI), part of the National Institutes of Health. The Molecular Profiling based Assignment of Cancer Therapeutics, or M-PACT, trial is one of the first to use a randomized trial design to assess if assigning treatment based on genetic screening can improve the rate and duration of response in patients with advanced solid tumors. A trial in which patients are randomly assigned to various treatment options is the gold-standard method for determining which treatment option is best.

Researchers hope that in addition to the knowledge gained from the trial about assigning therapy based on results of genetic sequencing of tumors, this trial could identify patient sub-groups that are likely to benefit from certain treatments and result in new treatments being developed quickly for some cancers. This could ultimately lead to smaller, more definitive clinical trials, which would be helpful to clinicians and patients in terms of cost and time.



MPACT Logo

M-PACT 4 Treatment Regimens, 3 Pathways, and 20 Targeted Genes		
RAS pathway: GSK 1120212 MEK inhibitor	Gain of Function <i>BRAF, KRAS</i> <i>NRAS, HRAS</i>	Loss of Function <i>NF1</i>
PI3K pathway: Everolimus mTOR inhibitor	<i>AKT1, PIK3CA,</i> <i>MTOR</i>	<i>PTEN</i> <i>FBXW7</i>
DNA repair pathways: Veliparib (PARP inhibitor) + TMZ		<i>ATM, ATR, ERCC1,</i> <i>MLH1, MSH2, NBN,</i> <i>RAD51</i>
MK1775 (Wee1 inhibitor) + carboplatin		<i>PARP1, PARP2,</i> <i>TP53</i>
<p style="text-align: right;">National Cancer Institute</p> <p style="text-align: center;"><u>391 aMOIs (with COSMIC ID) selected</u></p>		

NATIONAL CANCER INSTITUTE NCI-MATCH CLINICAL TRIAL

THIS PRECISION MEDICINE TRIAL
EXPLORES TREATING PATIENTS
BASED ON THE MOLECULAR
PROFILES OF THEIR TUMORS

NCI-MATCH* IS FOR ADULTS WITH:

- solid tumors (including rare tumors) and lymphomas
- tumors that no longer respond to standard treatment



ABOUT 3,000
CANCER PATIENTS
WILL BE
SCREENED WITH A
TUMOR BIOPSY



GENE SEQUENCING WILL LOOK FOR CHANGES IN 143 GENES

THE BIOPSIED
TUMOR TISSUE
WILL UNDERGO
GENE
SEQUENCING



IF A PATIENT'S TUMOR HAS A GENETIC ABNORMALITY THAT MATCHES ONE TARGETED BY A DRUG USED IN THE TRIAL, THE PATIENT WILL BE ELIGIBLE TO JOIN THE TREATMENT PORTION OF NCI-MATCH

CONTACT US ✉ SIGN IN 👤

TAPUR Targeted Agent and Profiling Utilization Registry Study
American Society of Clinical Oncology

FOR PATIENTS FOR RESEARCHERS PARTICIPATING CENTERS



Find out more about getting involved with TAPUR.

RESEARCH COLLABORATORS

About the TAPUR Study

The Targeted Agent and Profiling Utilization Registry (TAPUR) Study is a non-randomized clinical trial that aims to describe the performance (both safety and efficacy) of commercially available, targeted anticancer drugs prescribed for treatment of patients with advanced cancer that has a potentially actionable genomic variant. The study provides approved targeted therapies that are contributed to the program by collaborating pharmaceutical companies, catalogues the choice of genomic profiling test by clinical oncologists and aims to learn about the utility of registry data to develop hypotheses for additional clinical trials. To find responses to commonly asked questions, please visit our [FAQ page](#) and review our [patient brochure](#).

Who Benefits?

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The screenshot shows the 'FEATURES OF ALAMUT® VISUAL' page. The navigation bar includes 'ABOUT US', 'PRODUCTS', 'MEDIA CENTER', and 'CONTACT'. A 'REQUEST TRIAL' button is in the top right. The breadcrumb trail is 'Home > AlamuT Visual > Features'. A left sidebar lists 'FEATURES', 'DOCUMENTATION', 'EVALUATION', 'VIDEO TUTORIALS', and 'TECHNICAL SPECIFICATIONS'. The main content area is titled 'FEATURES OF ALAMUT® VISUAL' and describes the software as a reference tool for human variation interpretation. It lists 'MAIN FEATURES' such as a gene browser, single user interface, HGVS compliance, and various prediction tools. 'OTHER FEATURES' include database connectivity and file format support. 'AVAILABLE ANNOTATIONS' list various genomic and clinical data sources like phastCons, dbSNP, and COSMIC.

ABOUT US PRODUCTS MEDIA CENTER CONTACT

Home > AlamuT Visual > Features

REQUEST TRIAL

FEATURES OF ALAMUT® VISUAL

AlamuT® Visual, the reference software for human variation interpretation

FEATURES

DOCUMENTATION

EVALUATION

VIDEO TUTORIALS

TECHNICAL SPECIFICATIONS

MAIN FEATURES

- Gene browser supporting human genes (protein coding, non-protein coding and pseudogenes)
- A single user interface with relevant annotations gathered from public databases such as NCBI, EBI, UCSC
- HGVS nomenclature compliant software
- Mutation reporting with pathogenicity clues
- Calculates functional impact of variants with relevant prediction tools:
 - Splicing prediction tools (SpliceSiteFinder-like, MaxEntScan, NNSPLICE, GeneSplicer, Human Splicing Finder)
 - ESE tools
 - Missense prediction tools (Align GVGD, SIFT, MutationTaster, PolyPhen-2, KD4v)
- Advanced BAM NGS alignments viewer with VCF support

OTHER FEATURES

- Automatically connects to the well-curated AlamuT software suite database
- Manages and visualizes lab's variants
- Automatic form filling of web-based missense prediction tools
- Mutation-focused search engine over PubMed abstracts
- Manages and visualizes sequence-based private annotations (e.g. primers, probes)
- Uses standard bioinformatics file formats (e.g., VCF, BAM, BED, GFF)

AVAILABLE ANNOTATIONS

- Nucleotide conservation (phastCons and phyloP scores)
- Reference transcripts
- dbSNP, ExAC, ESP/EVS variants
- Genome of the Netherlands (GoNL), Japan Human Genetic Variation Database (HGVD)
- ClinVar, SwissProt pathogenic variants
- COSMIC variants (available at no extra cost to both academic and commercial users — users who wish to download the COSMIC database, manipulate or mine it directly would need to obtain it from the Sanger Institute)
- Integrates HGMD® Professional (requires a separate subscription from QIAGEN)
- Functional protein domains
- Orthologues alignments

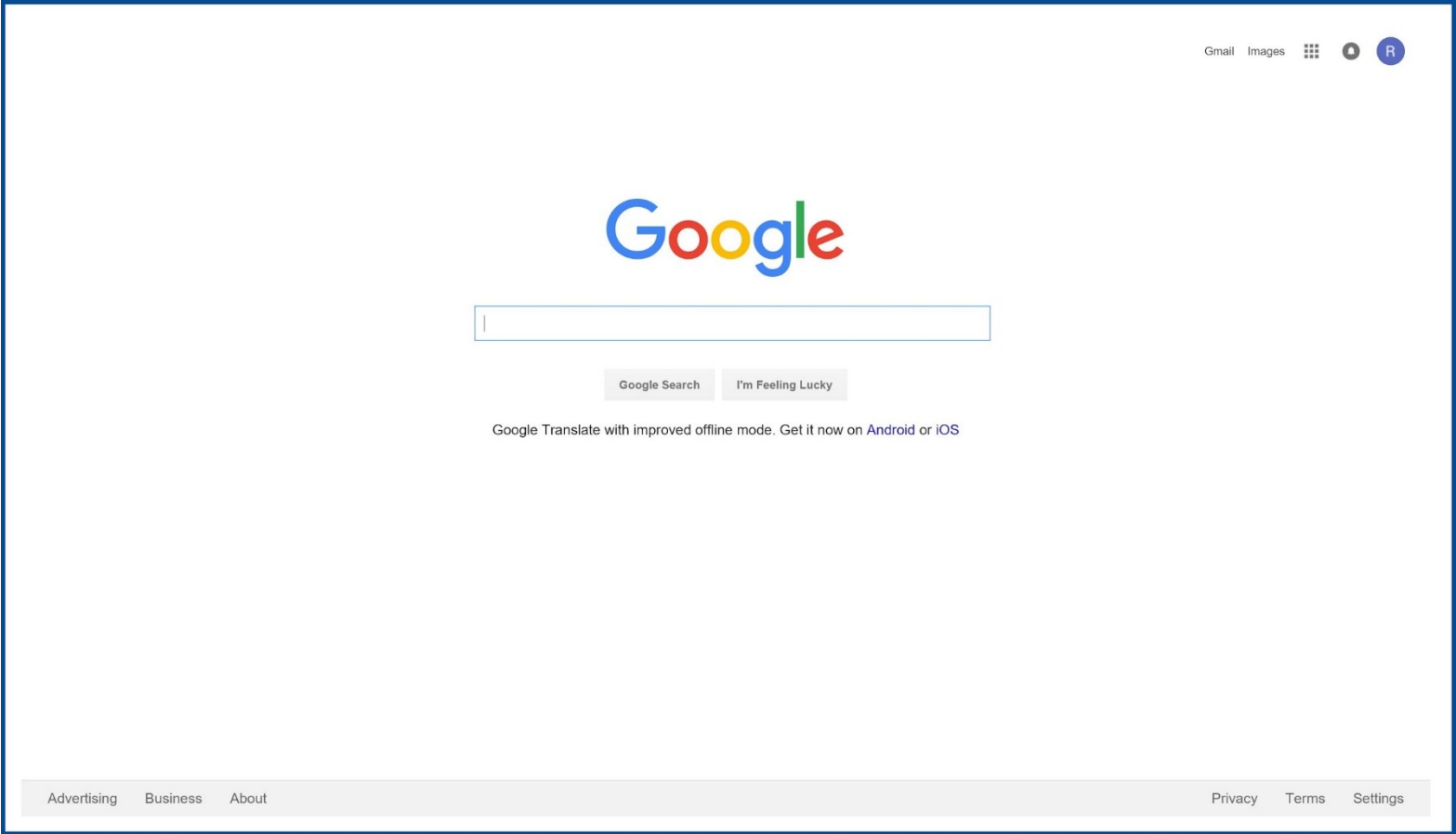
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Find a Cancer Mutation

Disease (required):

Gene (optional):

Variant (optional):

Due to changes in how the National Cancer Institute provides information about clinical trials, the My Cancer Genome clinical trials search and tabs will not be available until further notice. For information about cancer clinical trials, please visit the following resources:

- For all cancer-related clinical trials, both open for enrollment and closed, see ClinicalTrials.gov and search for cancer or other relevant search terms.
- For open and enrolling NCI-funded cancer clinical trials, see Cancer.gov.

[Learn About My Cancer Genome](#) ▶

Support My Cancer Genome



Help create new tools and resources

[More...](#)

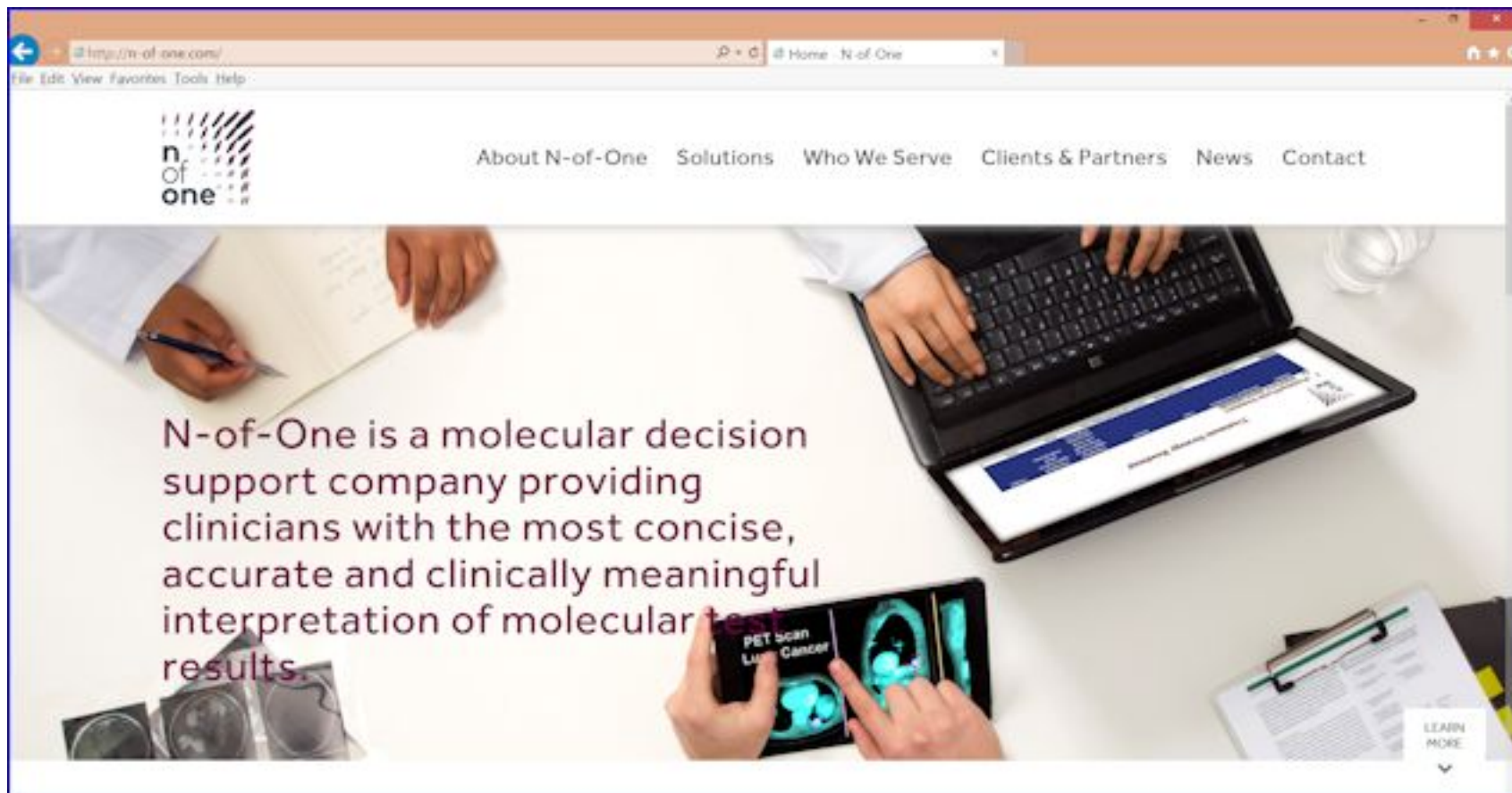
Molecular Medicine

- ▶ [Pathways](#)
- ▶ [Immunotherapy in Cancer](#)
- ▶ [Overview of Targeted Therapies for Cancer](#)
- ▶ [List of Anticancer Agents](#)
- ▶ [Types of Molecular Tumor Testing](#)

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REFINE BY:

- Location
- Any location
 - United States
 - State
 - Within miles of

Gene

- PI3K
- PIK3CA
- PTEN
- AKT
- [Show more...](#)

Mutation

- HER-2 Loss
- ER Amplification
- ER/PR positive
- [Show more...](#)

Patient has/is

- Infection
- Pregnant
- Breast feeding
- Heart failure
- Heart attack
- [Show more...](#)

Condition

- Breast cancer
- Lymphoma
- Hormone Receptor Positive Breast Cancer
- [Show more...](#)

Drug

- Bkm-120
- Byl719
- Everolimus
- [Show more...](#)

Drug Class

- [Show more...](#)

Resistance

- [Show more...](#)

Institution

- [Show more...](#)

Phase

- [Show more...](#)

Trial type

- Interventional**
- [Show more...](#)

Status

- Enrolling**
- [Show more...](#)

PIK3CA



HIDE OPTIONS

Showing **Interventional** and **Enrolling** trials and drugs specific to **PIK3CA**.

MATCHING DRUGS | FDA 2

Confidence **High** Medium Low

<p>TEMSIROLIMUS FDA</p> <p>Brand: Torisel FDA Approved for ... Molecular Targets ...</p> <p>Progressed On? Find Trials With This Drug</p> <p>SHOW MORE ABOUT THIS DRUG</p>	<p>EVEROLIMUS FDA</p> <p>Brand: Afinitor FDA Approved for ... Molecular Targets ...</p> <p>Progressed On? Find Trials With This Drug</p> <p>SHOW MORE ABOUT THIS DRUG</p>	<p>BKM-120</p> <p>Molecular Targets Studied PIK3CA PIK3CG Show More Targets...</p> <p>Progressed On? Find Trials With This Drug</p> <p>SHOW MORE ABOUT THIS DRUG</p>	<p>TASELISIB</p> <p>Conditions Studied Breast cancer Molecular Targets Studied PIK3CA PIK3CB Show More Targets...</p> <p>Progressed On? Find Trials With This Drug</p> <p>SHOW MORE ABOUT THIS DRUG</p>
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MATCHING TRIALS | 168

<p>NCT02340221 - SANDPIPER Study: A Study Of Taselisib + Fulvestrant Versus Placebo + Fulvestrant In Patients With Advanced or Metastatic Breast Cancer Who Have Disease Recurrence or Progression During or After Aromatase Inhibitor Therapy</p> <p>Alteration: PIK3CA 79 of 125 sites: recruiting</p> <p>Type: Interventional</p>	<p>Phase: 1 2 3 4</p> <p>Report a problem</p>
<p>NCT01633060 - A Phase III Study of BKM120 With Fulvestrant in Patients With HR+,HER2-, AI Treated, Locally Advanced or Metastatic Breast Cancer Who Progressed on or After mTORi</p> <p>Alteration: PIK3CA 182 of 265 sites: recruiting</p> <p>Type: Interventional</p>	<p>Phase: 1 2 3 4</p> <p>Report a problem</p>
<p>NCT02154490 - Lung-MAP: S1400 Biomarker-Targeted Second-Line Therapy in Treating Patients With Recurrent Stage IIIB-IV Squamous Cell Lung Cancer</p> <p>Alteration: PIK3CA 552 of 558 sites: recruiting</p> <p>Type: Interventional</p>	<p>Phase: 1 2 3 4</p> <p>Report a problem</p>
<p>NCT02506556 - Phosphatidylinositol 3-kinase (PI3K) Alpha iNhibition In Advanced Breast Cancer</p> <p>Alteration: PIK3CA 1 of 1 sites: recruiting</p> <p>Type: Interventional</p>	<p>Phase: 1 2 3 4</p> <p>Report a problem</p>



Cleveland Clinic

Every life deserves world class care.