Cleveland Clinic

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

August 30, 2016

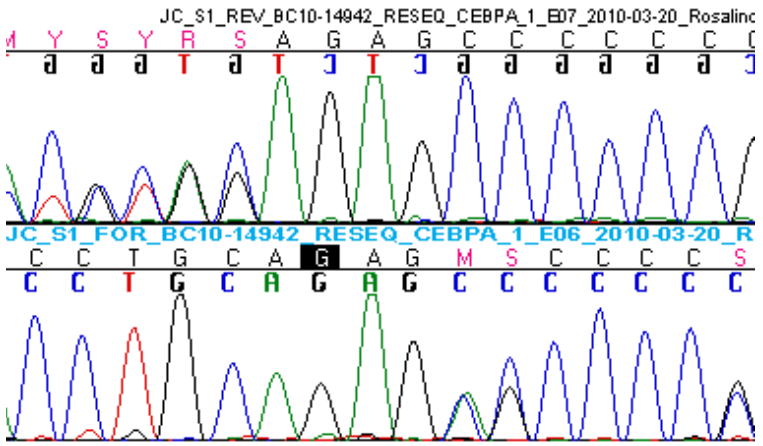
Roger D. Klein, MD JD

Medical Director, Molecular Pathology

Precision Medicine

Diagnosis

Prognosis



Response to Therapy

Side Effects

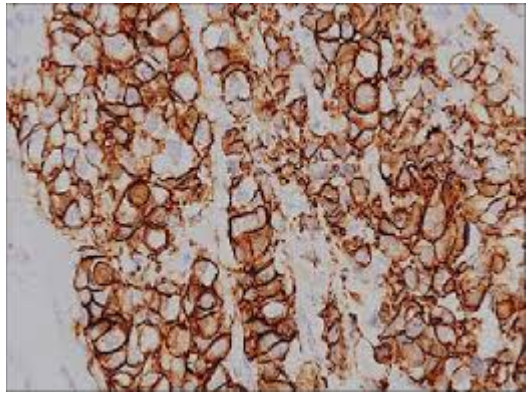
‘The right drug, for the right patient, at the right dose, at the right time’

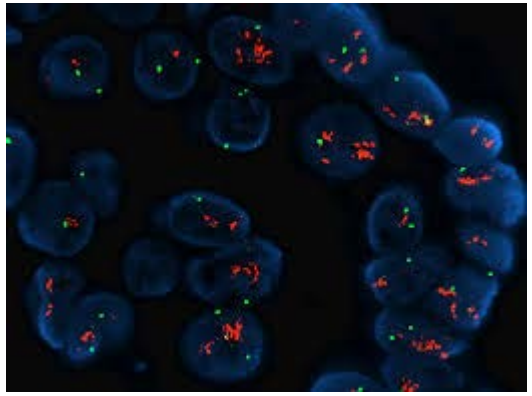
PRESENTED BY: Roger D. Klein, MD JD, Cleveland Clinic

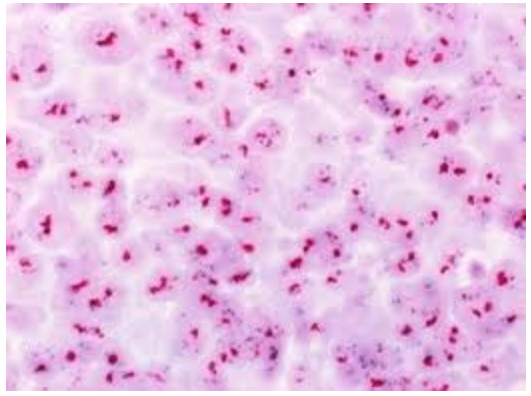
Traditional Analysis

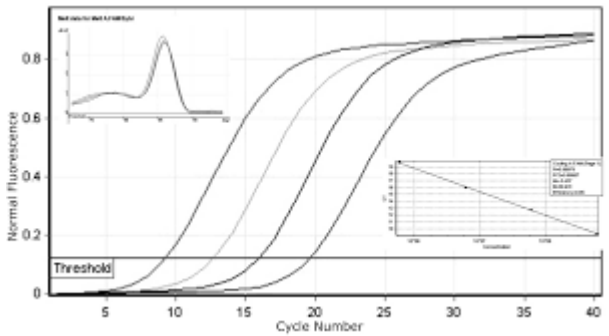
- Tumor type and marker specific
- IHC, ISH, PCR
- Single or small number of markers
- Highly specific, limited information

HER2 (ERBB2)

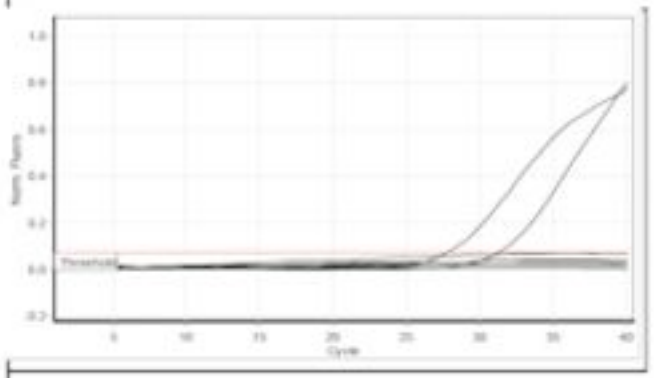







Normal Fluorescence
0.8
0.6
0.4
0.2
0
Threshold
5
10
15
20
25
30
35
40
Cycle Number

lung | FFPET | EGFR mutation detected



EGFR Genotype:

L858R

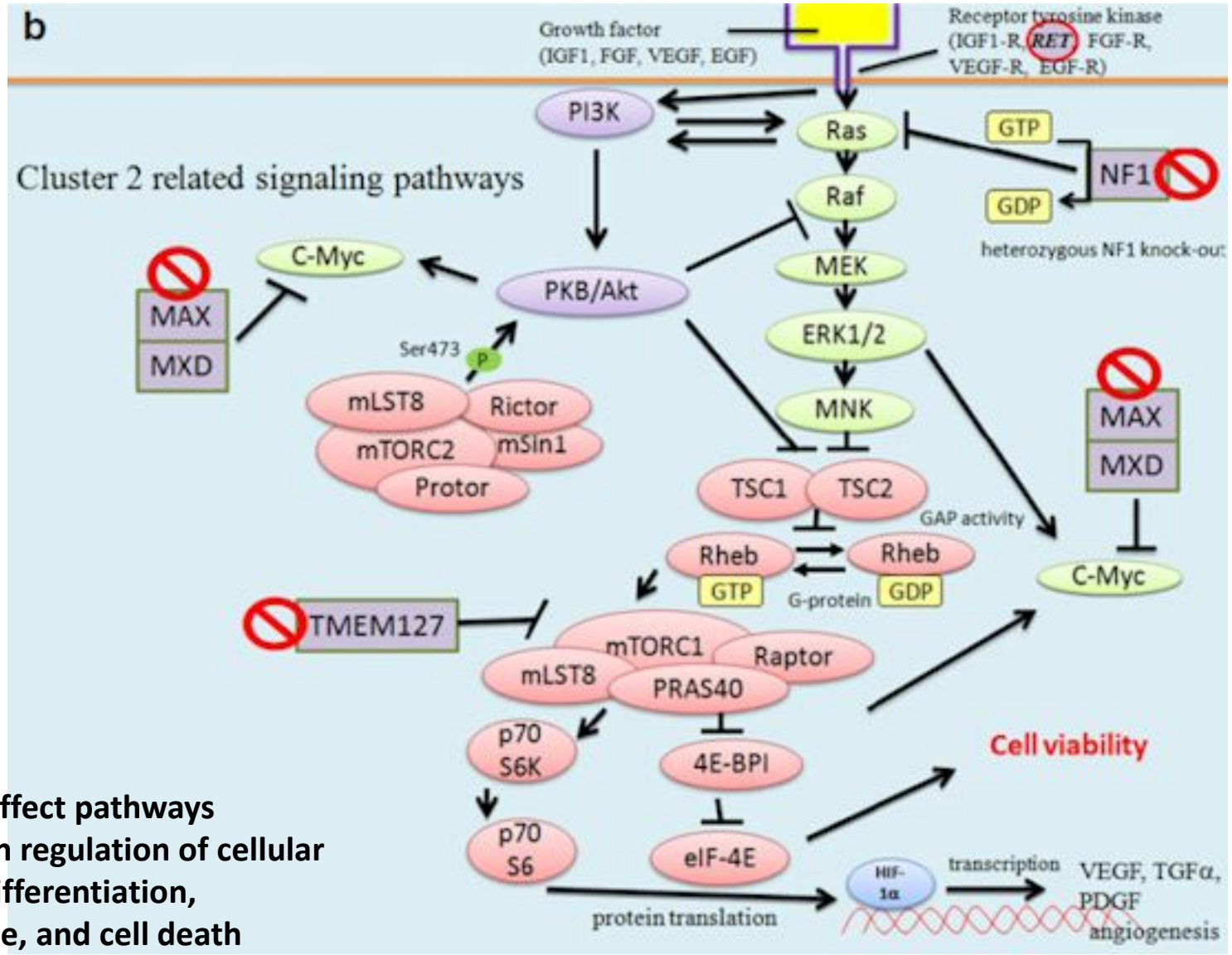
Mutation Reaction	C_T	ΔC_T	ΔC_T reference range *
Control Mix	27.88		
T790M			mutation detected if ΔC_T <0.38
Del (exon 19)			mutation detected if ΔC_T <0.06
L858R	31.42	3.54	mutation detected if ΔC_T <8.58
L861Q			mutation detected if ΔC_T <9.26
G719X			mutation detected if ΔC_T <9.31
S768I			mutation detected if ΔC_T <9.26
Ins (exon 20)			mutation detected if ΔC_T <7.91

* = when true amplification (sigmoidal curve) has occurred, not non-specific amplification (linear curve)

Comments: The specimen submitted for analysis contained 20% tumors cells

The missense 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 50 fold more activity compared to wild type EGFR receptors. (references: 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

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

FOUNDATIONONE™ | FOUNDATION MEDICINE®

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

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

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

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?

UnitedHealthcare®

UnitedHealthcare® Commercial
Medical Policy

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.

  - **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.

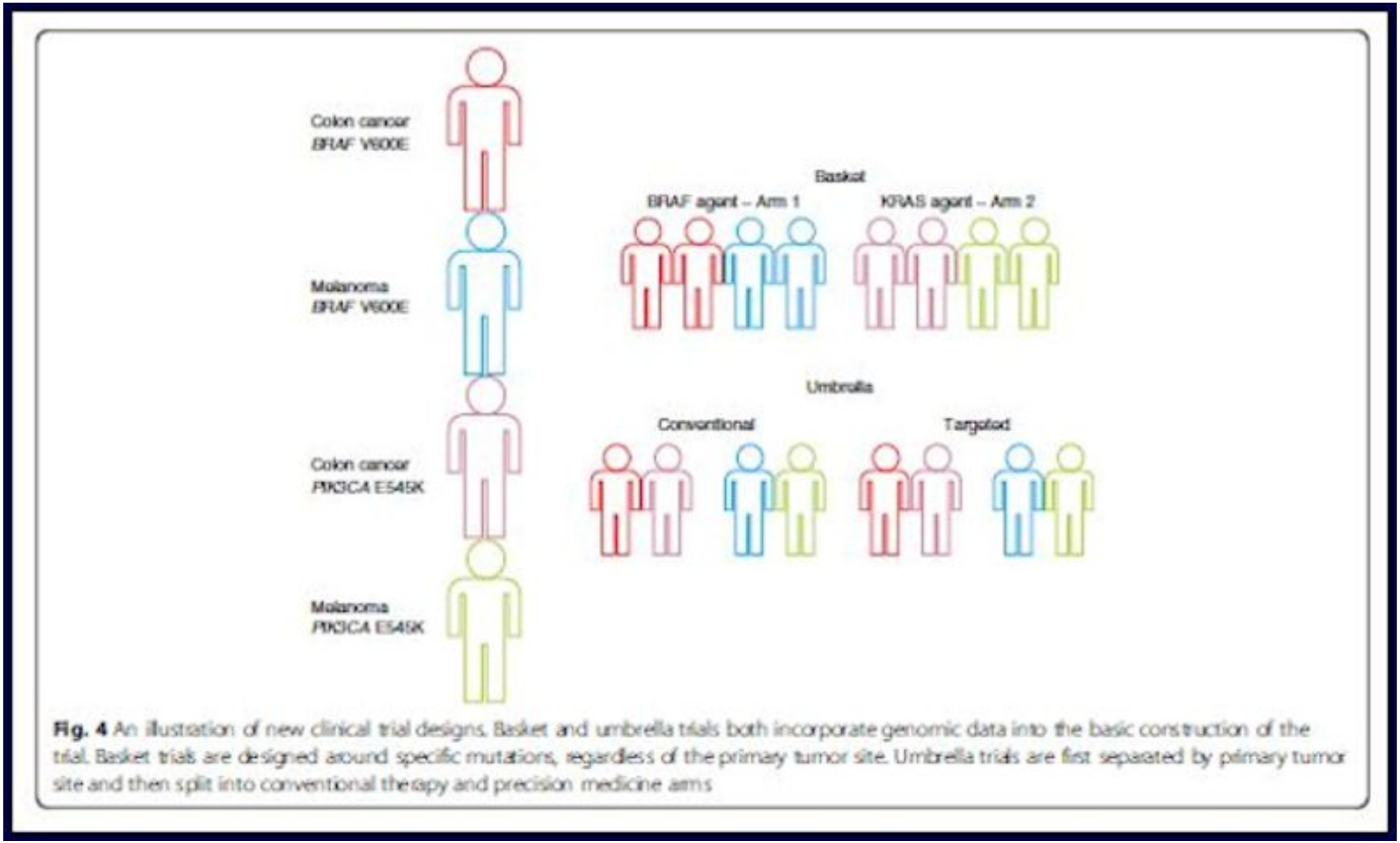


Fig. 4 An illustration of new clinical trial designs. Basket and umbrella trials both incorporate genomic data into the basic construction of the trial. Basket trials are designed around specific mutations, regardless of the primary tumor site. Umbrella trials are first separated by primary tumor site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

NIH NATIONAL CANCER INSTITUTE

Español

1-800-4-CANCER Live Chat Dictionary

ABOUT CANCER | CANCER TYPES | RESEARCH | GRANTS & TRAINING | NEWS & EVENTS | ABOUT NCI | search

Home > News & Events > Press Releases > 2014

PRESS RELEASES

NCI Press Release

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

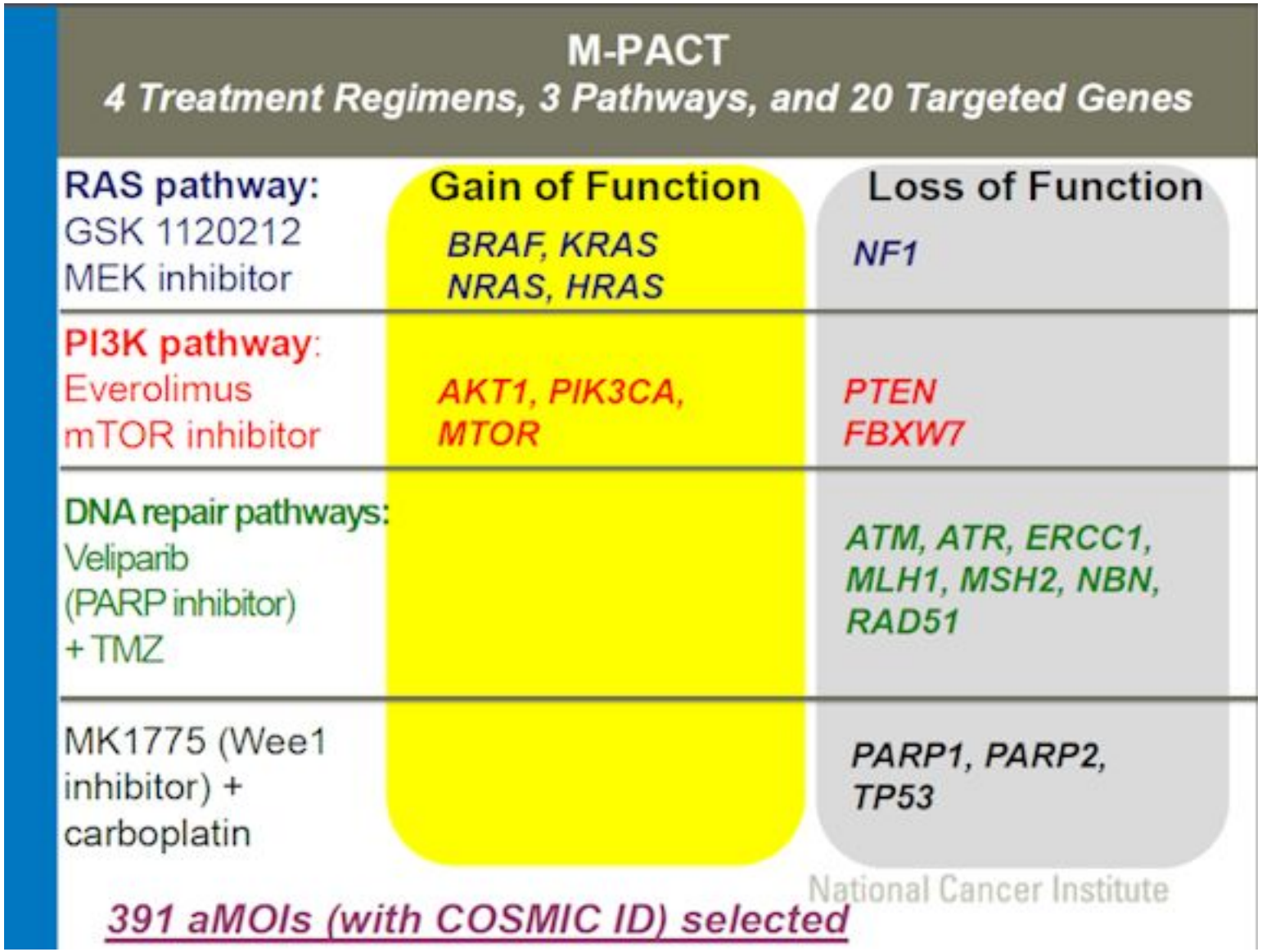
Posted: January 30, 2014

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.

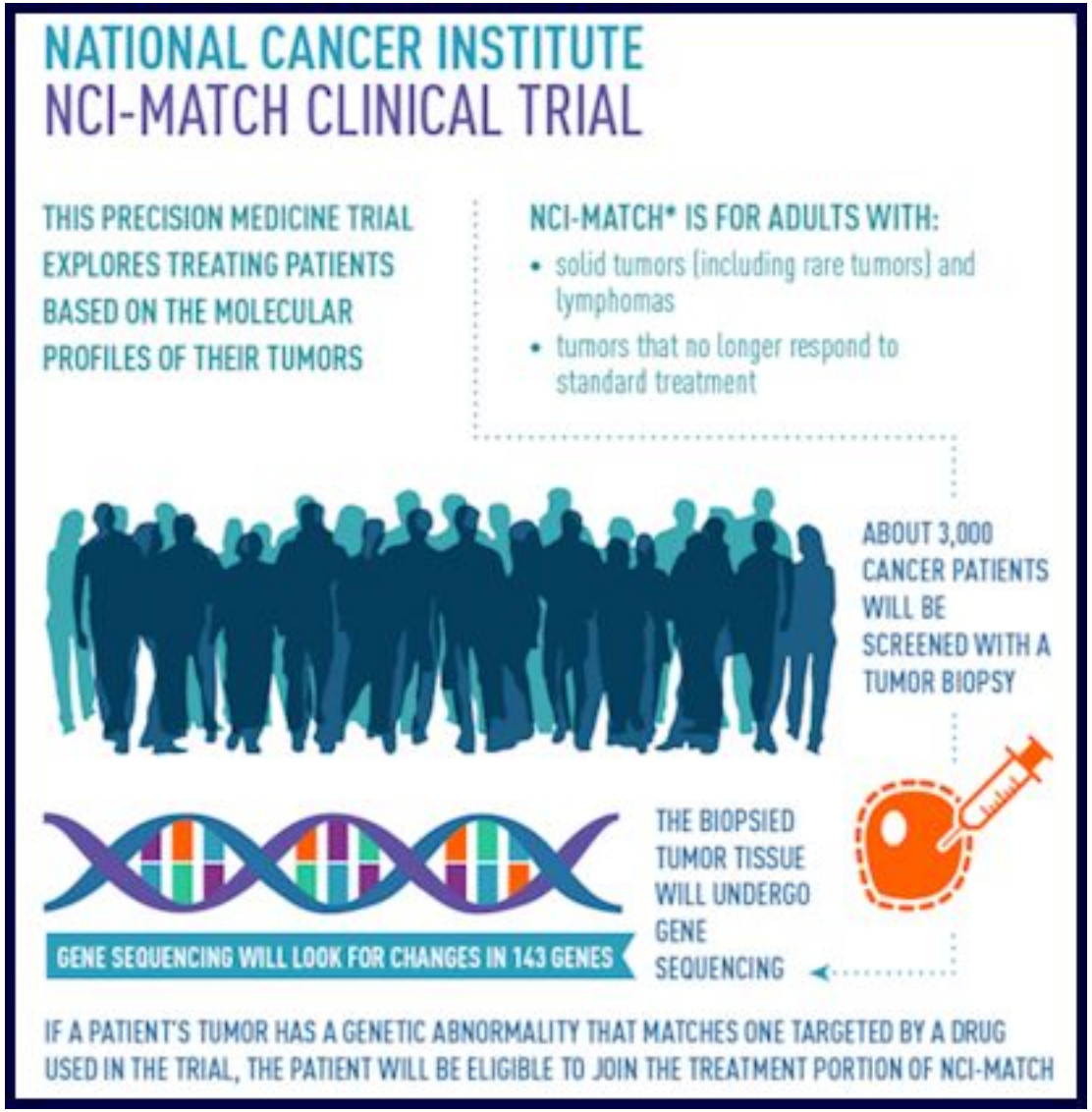
MPACT Logo

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.

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

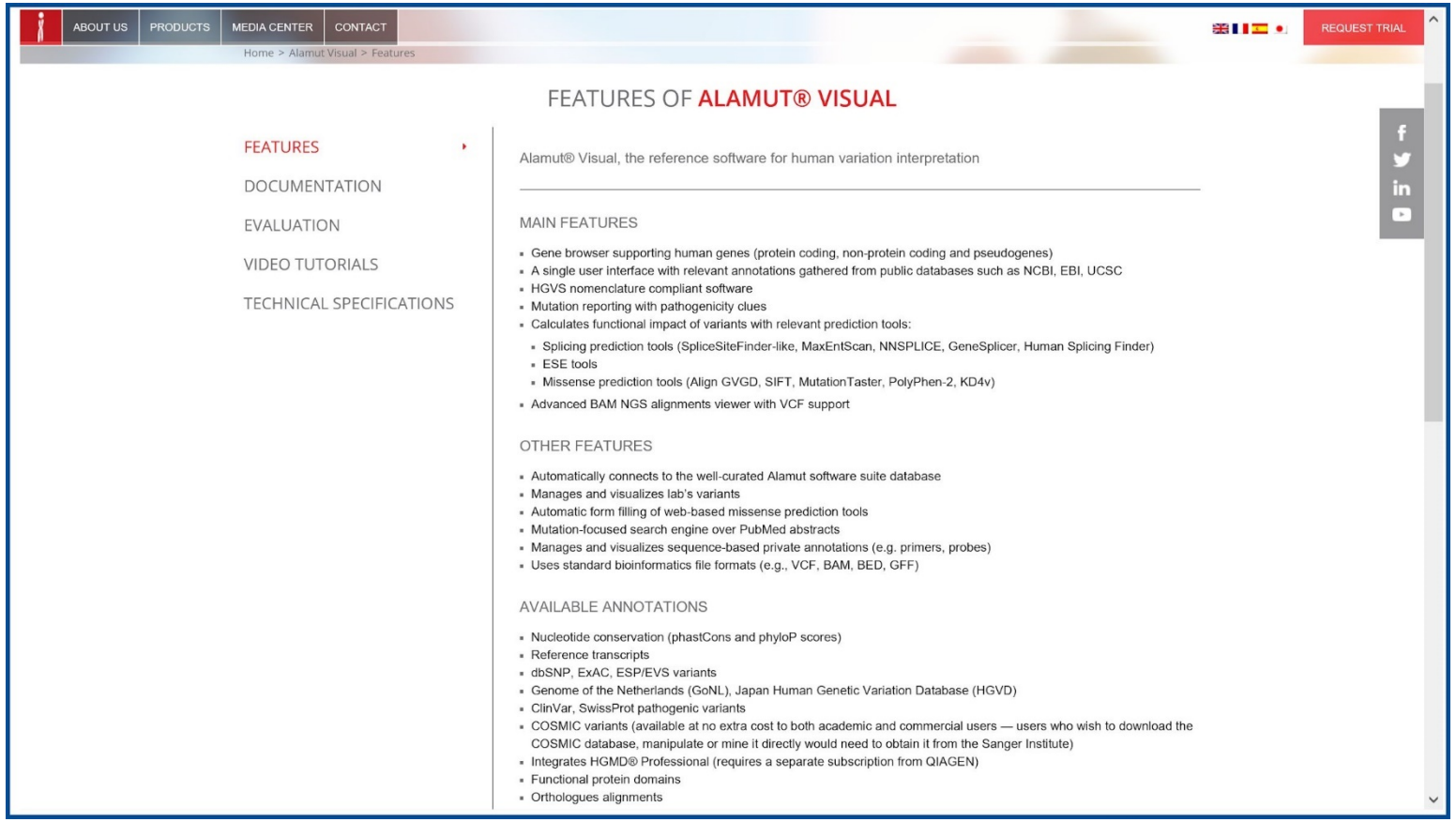


PRESENTED BY: Roger D. Klein, MD JD, Cleveland Clinic

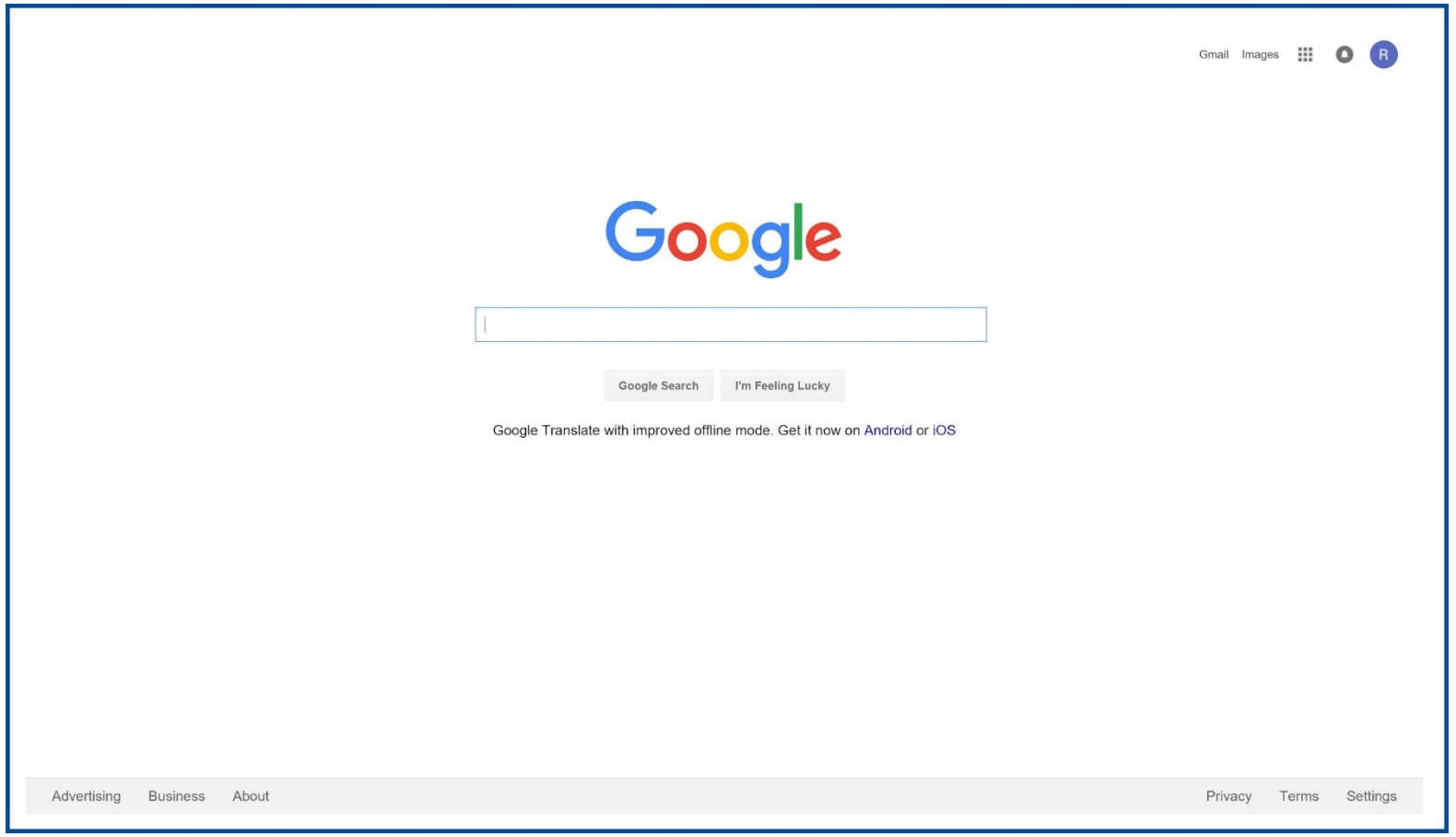


PRESENTED BY: Roger D. Klein, MD JD, Cleveland Clinic

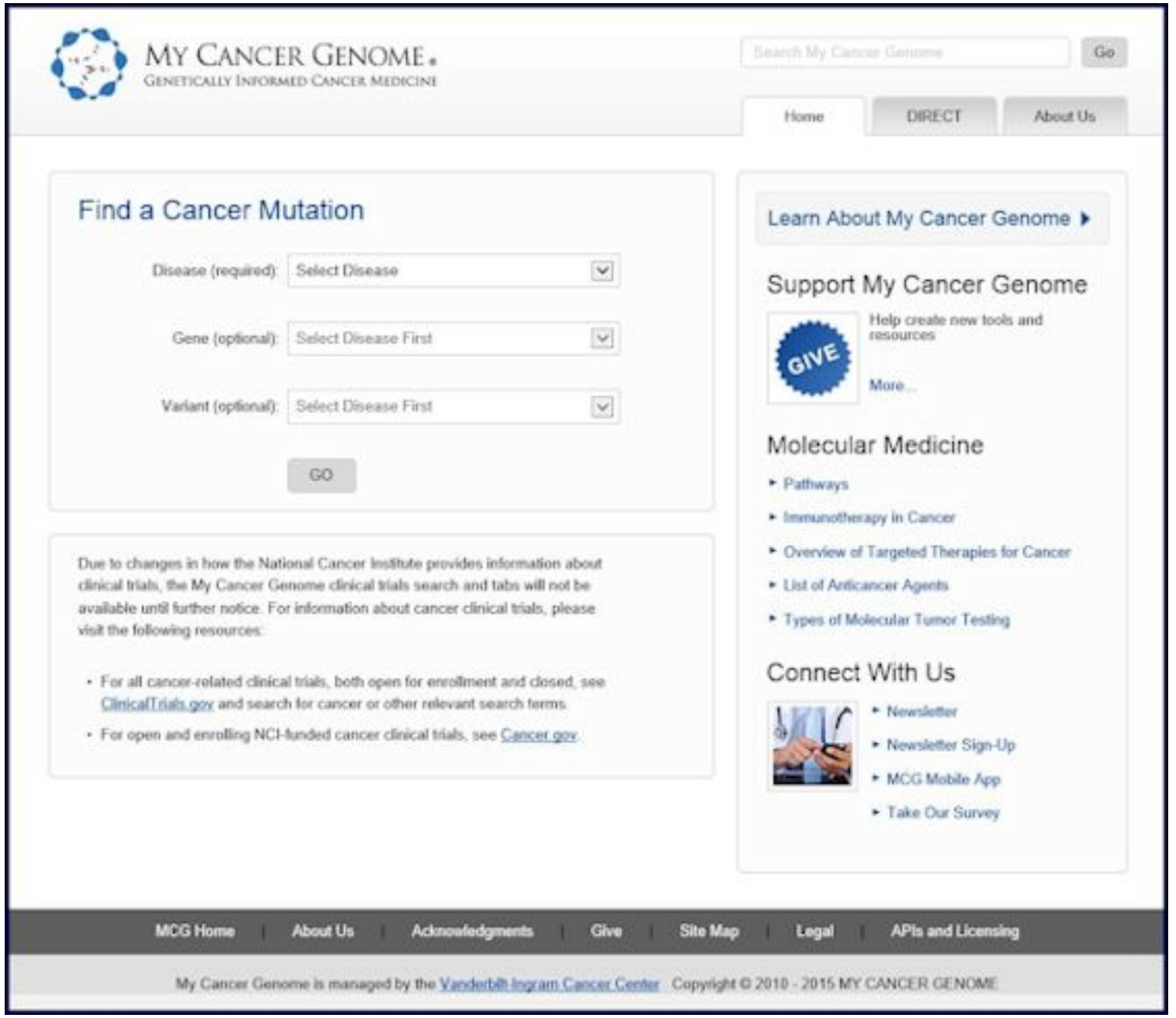

CONTACT US
SIGN IN
TAPUR
Targeted Agent and Profiling Utilization Registry Study
FOR PATIENTS
FOR RESEARCHERS
PARTICIPATING CENTERS
Find out more about getting involved with TAPUR.
RESEARCH COLLABORATORS
About the TAPUR Study
The Targeted Agent and Profiling Utilization Registry (TAPUR) Study is a non-randomized 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?



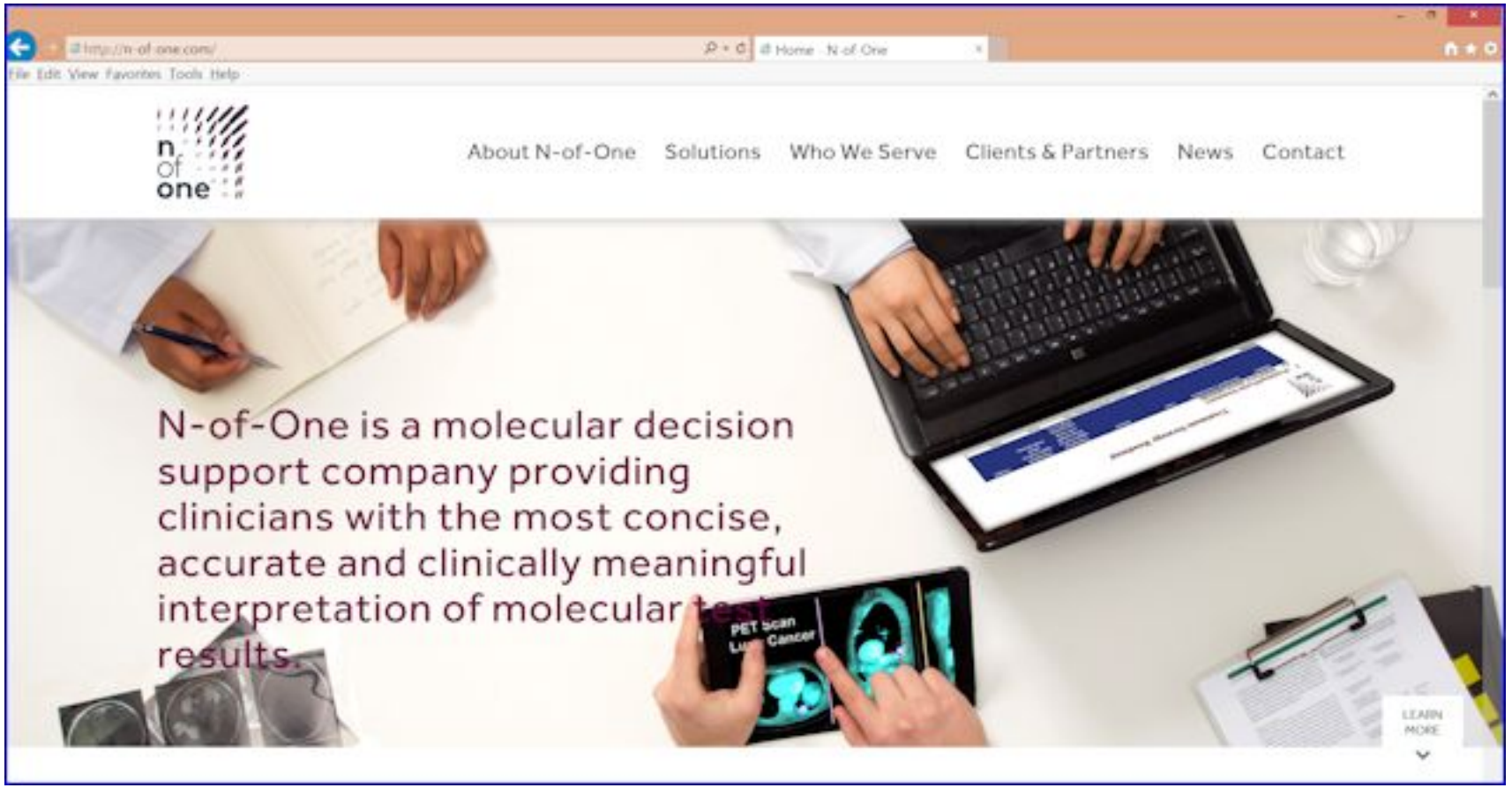
PRESENTED BY: Roger D. Klein, MD JD, Cleveland Clinic



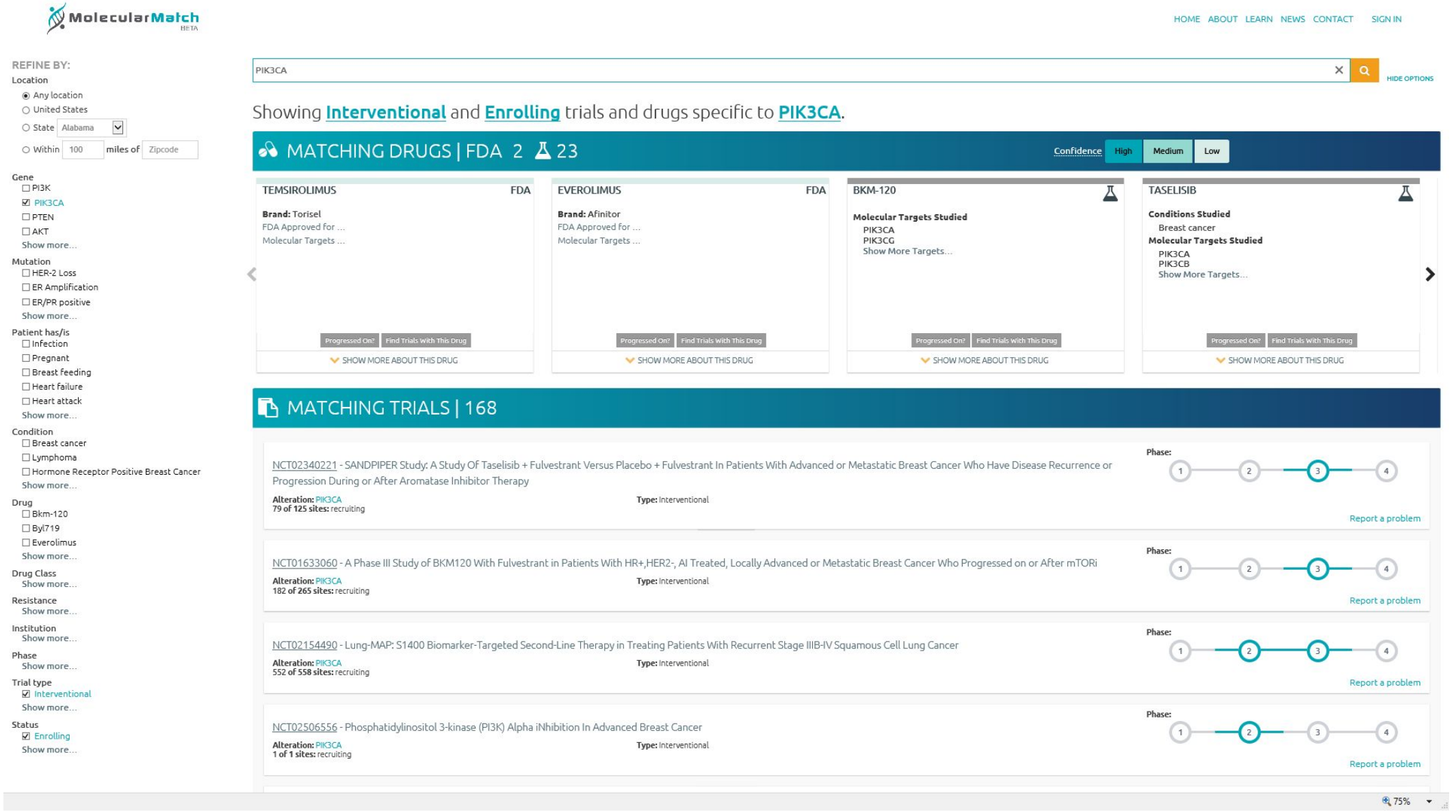
PRESENTED BY: Roger D. Klein, MD JD, Cleveland Clinic



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



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



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

Cleveland Clinic

Every life deserves world class care.