The Next Frontier: Personalized Medicine and Cancer

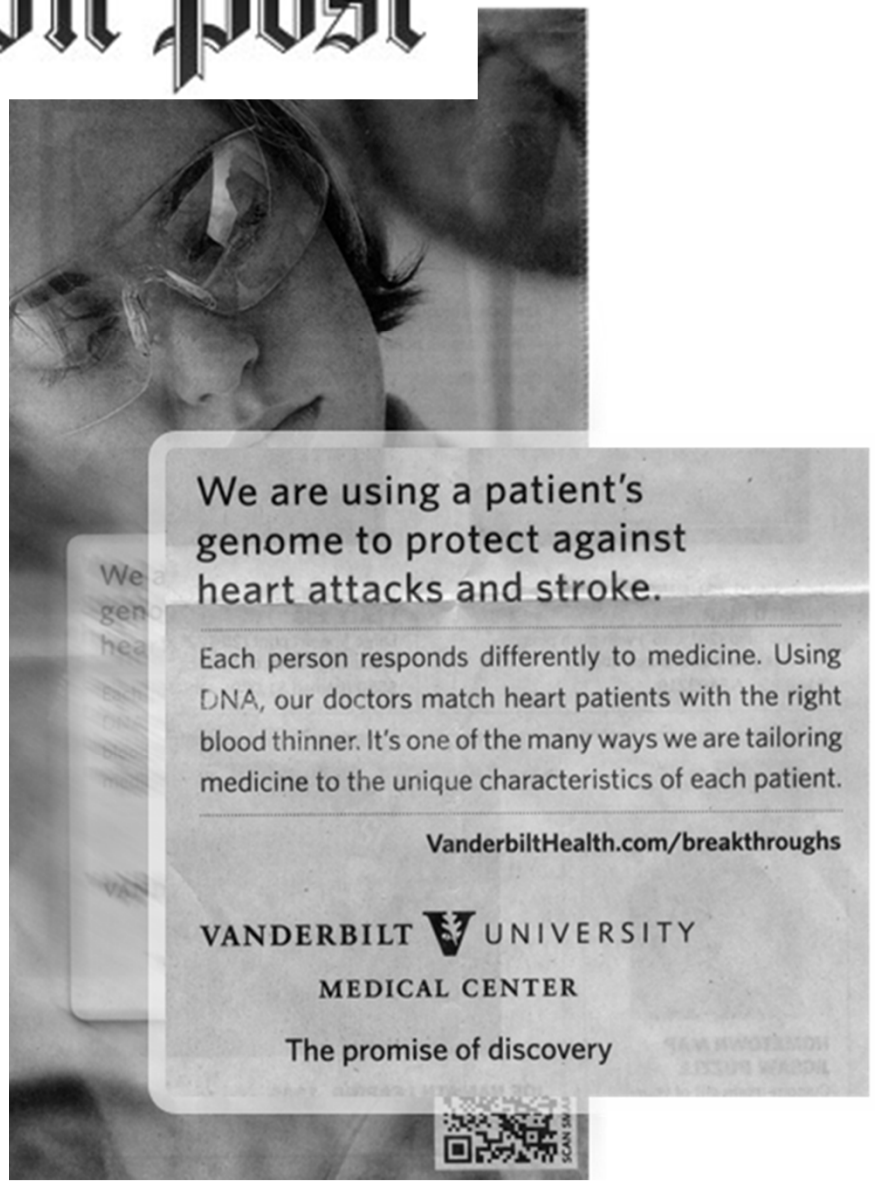
Ken Buetow, Ph.D.

Director Computational Science and Informatics Core Program,
Complex Adaptive Systems Initiative
Arizona State University

MDx Next Spring 2012
Gaining the MDx Edge: Putting Molecular Diagnostics to Work in the Clinical Lab


FUTURE
PAST
PRESENT
The future is already here…
it just not evenly distributed.
William Gibson

The Washington Post



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General Information | My Health at Vanderbilt | Conditions, Diseases and Procedures | Information about a Doctor | Giving | Healthcare Breakthroughs | Quality Answers

Video: Making Medicine Work for Each Person

Vanderbilt University Medical Center
The Promise of Discovery

Discovery science is like "pulling back a curtain" to see what's behind it. You then find something completely new. You find something that nobody has seen before. At Vanderbilt University Medical Center, discovery science is "pulling back curtains" in the major diseases and conditions of our time.

Learn more about how Vanderbilt is reshaping healthcare.

- Developing new surgical tools
- New hope for people with melanoma
- Fighting lung cancer with molecular medicine
- Using genetics for smarter prescriptions

Learn about Vanderbilt's DNA databank

Vanderbilt BioVU

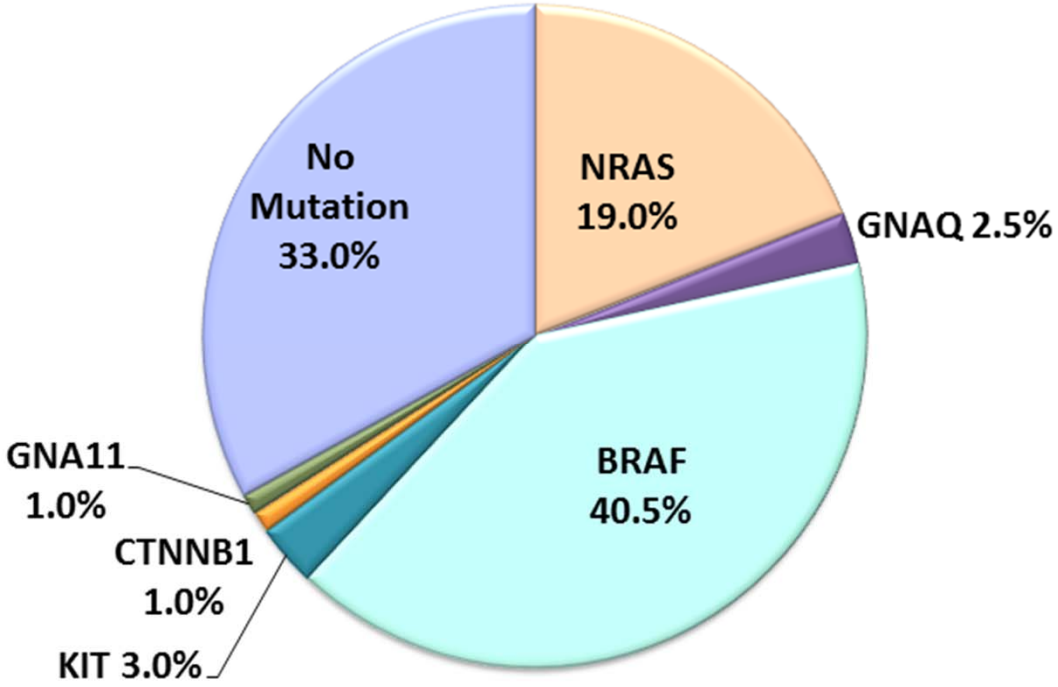
Vanderbilt-Ingram Cancer Center Personalized Cancer Medicine Initiative

7/1/10-10/31/11

Melanoma Panel: 538 patients

67% Patients with Actionable Mutation

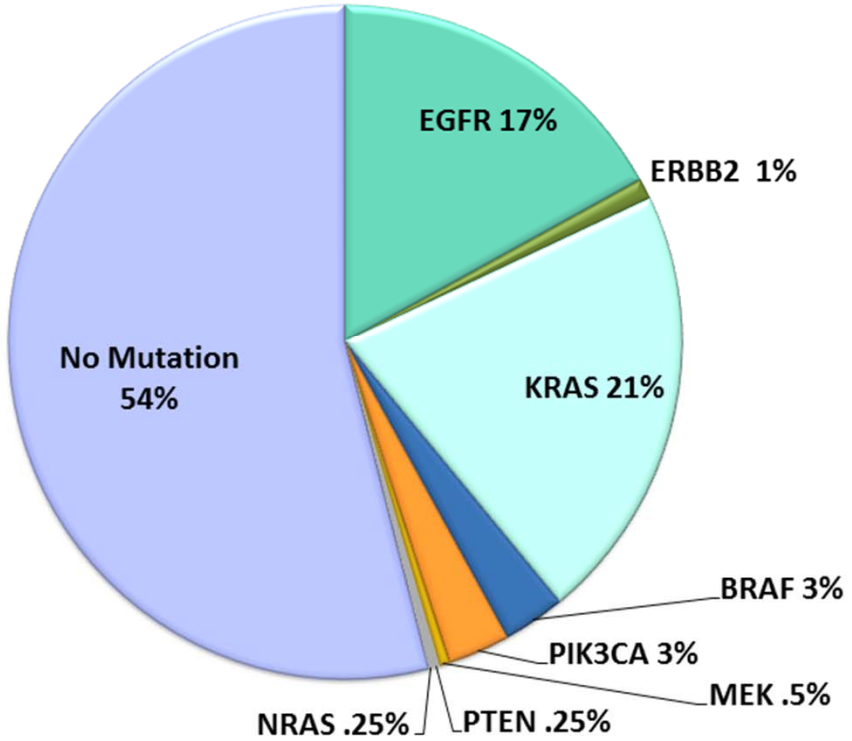
33% No Mutation Identified



Lung Panel: 451 patients

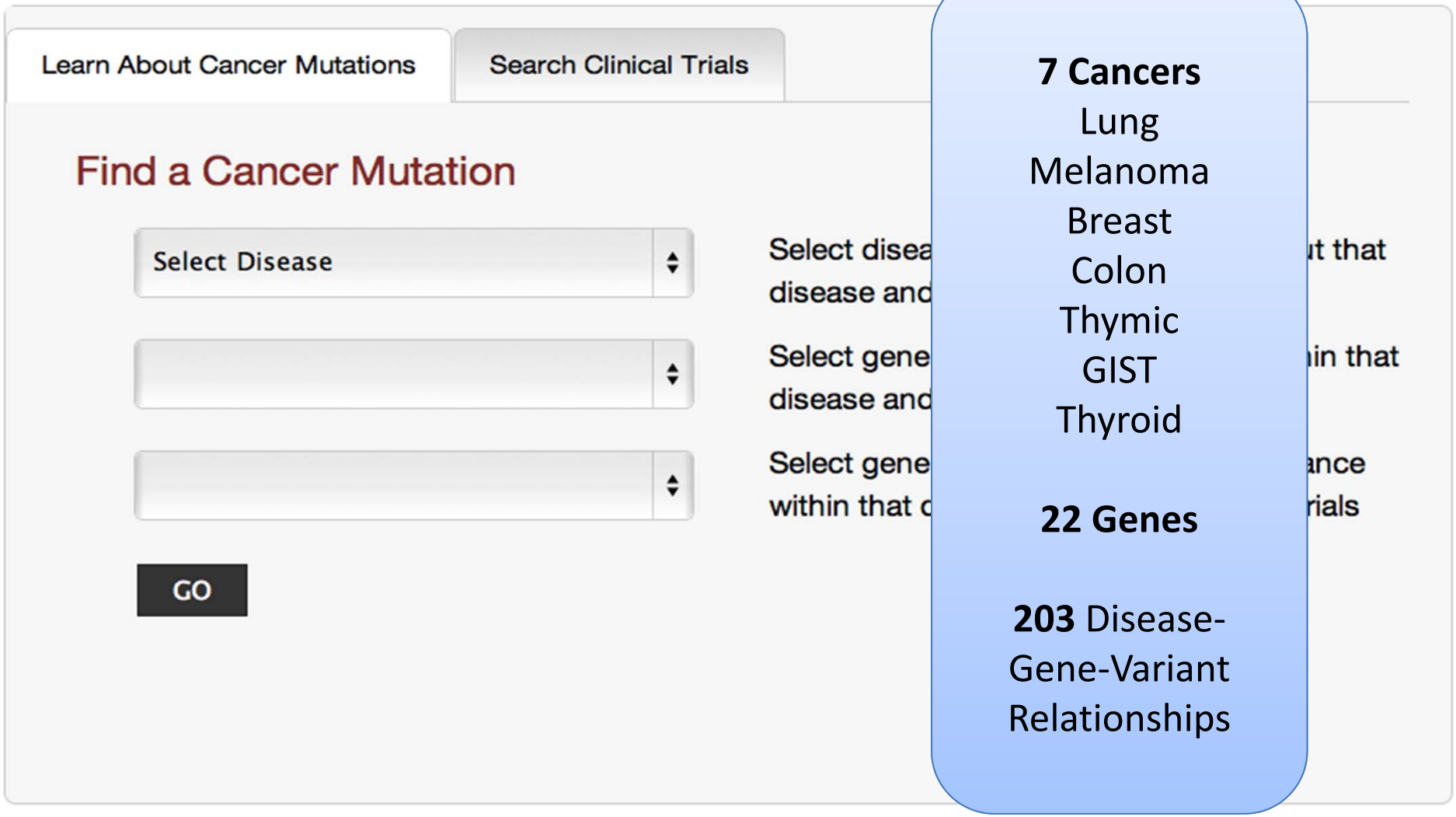
46% Patients with Actionable Mutation

54% No Mutation Identified



My Cancer Genome

Genetically informed cancer medicine - the next standard of care



VANDERBILT UNIVERSITY MEDICAL CENTER

Courtesy Mia Levy

Vanderbilt-Ingram Cancer Center

MR#	Patient Name	Actions	Tumor Gene Mutations: H-SMP	BRAF	CTNNB1	GNA11	GNAQ	KIT	NRAS
03 81	A, B M.	Actions	■	■					
03 56	A, P	Actions	■		■				■
03 35	B, J A	Actions	■						■
01 80	B, S A	Actions							
02 29	E, J E	Actions	■					■	
02 27	F, R M	Actions							
02 77	G, T	Actions							
02 73	H, A	Actions	■			■			
03 64	S, C	Actions	A						
02 79	S, A S	Actions	R						
02 40	W, J E I	Actions							
03 74	W, C L	Actions	■	■					

BRAF c.1798_1799GT>AG (V600R) Not Detected
BRAF c.1798_1799GT>AA (V600K) Not Detected
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BRAF c.1799_1800TG>AT (V600D) Not Detected

- Melanoma Overview
- BRAF
  - BRAF c.1798_1799GT>AG (V600R)
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  - BRAF c.1799_1800TG>AT (V600D)
- CTNNB1
- GNA11
- GNAQ
- KIT
- NRAS

- Other Cancers

- Molecular Pathology
- Take Our Survey
- Glossary
- News
- Our Team
- Acknowledgments

BRAF V600E (c.1799T>A) mutation in Melanoma

What is BRAF? | BRAF in Melanoma | BRAF V600E mutation | Clinical Trials

BRAF c.1799T>A (V600E) mutation in Melanoma

BRAF V600E mutation	
Properties	
Location of mutation	Kinase domain (exon 15)
Frequency of BRAF V600E	~85-90% of BRAF mutant melanoma
Implications for Targeted Therapeutics	
Response to BRAF inhibitors	Confers increased sensitivity*
Response to MEK inhibitors	Uncertain at this time#
Response to KIT inhibitors	Uncertain at this time

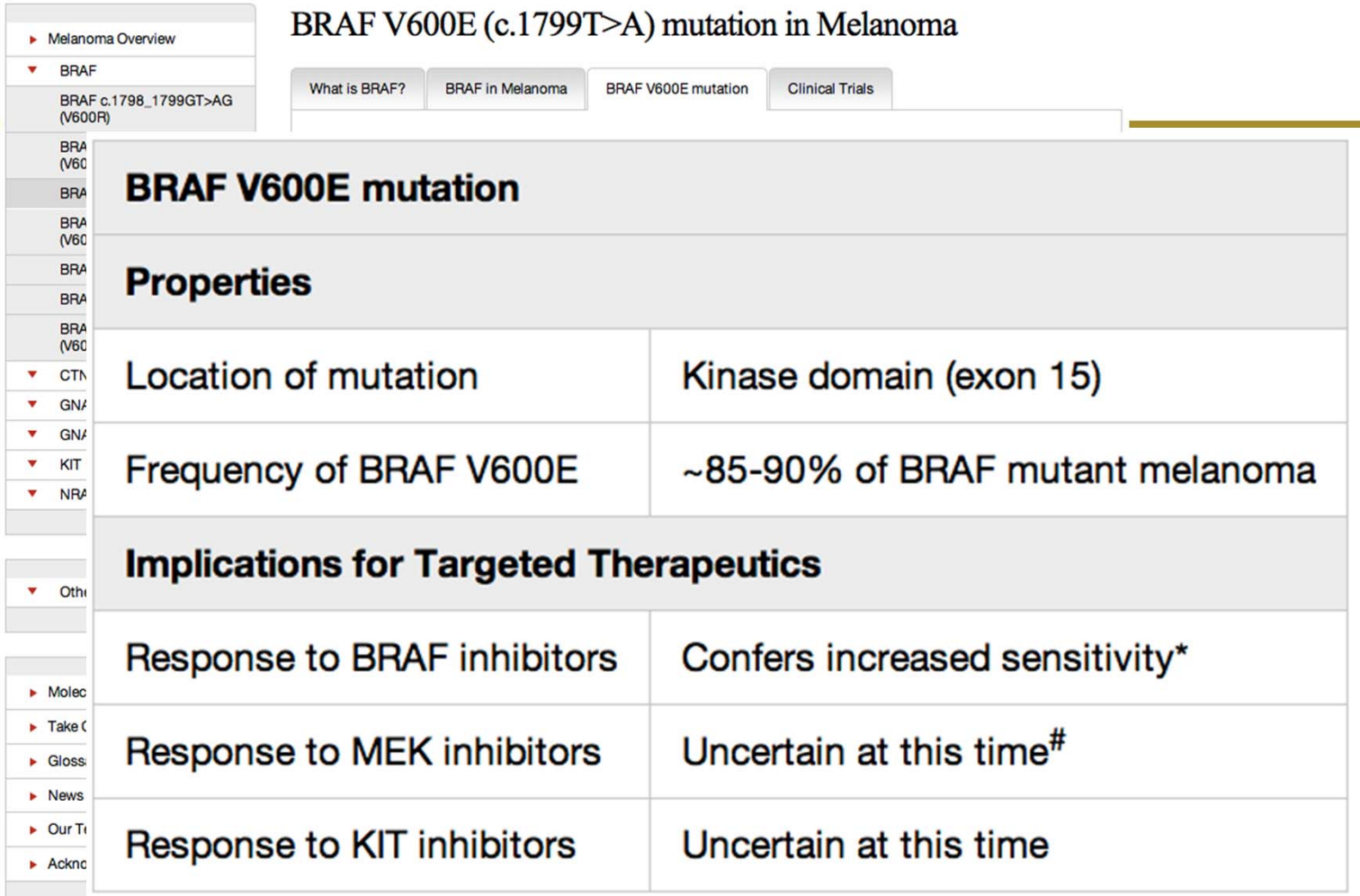
The V600E mutation results in an amino acid substitution at position 600 in BRAF, from a Valine (V) to a glutamic acid (E). This mutation occurs within the activation segment of the kinase domain **(Fig. 2)**. Approximately 70-90% of V600 BRAF mutations are V600E (Rubinstein, 2010). Mutant BRAF proteins have increased kinase activity and are transforming in vitro (Davies, 2002). BRAF mutations are usually found in tumors wildtype for NRAS, KIT, and other driver mutations.

Figure 2: Schematic of BRAF V600E mutation. Functional domains of BRAF are depicted. CR1: conserved regions 1. CR2: conserved region 2.

*In the initial phase I trial, patients with metastatic melanoma whose tumor harbored a BRAF V600E mutation displayed an 81% response rate to vemurafenib (PLX4032), an orally available inhibitor of mutated BRAF. The estimated progression-free survival was > 7 months and overall survival had not been reached at the time of study publication (Flaherty, 2010). In the follow-up randomized phase III trial comparing vemurafenib to dacarbazine in previously untreated, metastatic melanoma with the BRAF V600E mutation, vemurafenib improved rates of overall survival and progression-free survival (Chapman, 2011).

#Pre-clinical data has correlated the presence of activating mutations in BRAF with sensitivity to non-ATP competitive MEK inhibitors, AZD6244 and CI-1040 (Davies, 2007; Solit, 2006). In a Phase II clinical trial of AZD6244 versus temozolomide, 5 of 42 melanoma patients with BRAF V600E mutation had confirmed partial responses (12% objective response rate) (Dummer, 2008).

BRAF V600E mutation								
Treatment Agent	Drug Class	Line of Treatment	# pts in study	Response Rate	PFS (months)	OS (months)	Level of evidence	Reference
vemurafenib (PLX4032)	Mutated BRAF TKI^	1st to >3rd	32^	81%	> 7 months (estimated)	Not reached	II-1	(Flaherty, 2010)
vemurafenib (PLX4032)	Mutated BRAF TKI^	1st	337	48%	5.3	84% at 6 mos	I	(Chapman, 2011)
dacarbazine	Cytotoxic chemotherapy	1st	338	5%	1.6	64% at 6 mos	I	(Chapman, 2011)



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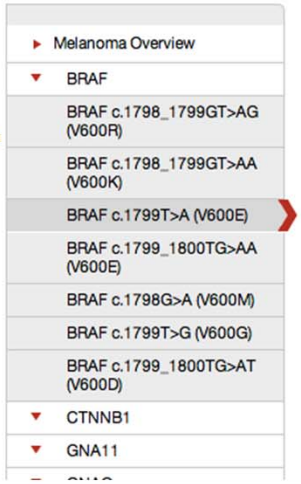
My Cancer Genome



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N Engl J Med. 2010 Aug 26;363(9):809-19.

Inhibition of mutated, activated BRAF in metastatic melanoma.

Flaherty KT, Puzanov I, Kim KB, Ribas A, McArthur GA, Sosman JA, O'Dwyer PJ, Lee RJ, Grippo JF, Nolop K, Chapman PB.

Abramson Cancer Center of the University of Pennsylvania, Philadelphia, USA. kflaherty@partners.org

Abstract

BACKGROUND: The identification of somatic mutations in the gene encoding the serine-threonine protein kinase B-RAF (BRAF) in the majority of melanomas offers an opportunity to test oncogene-targeted therapy for this disease.

METHODS: We conducted a multicenter, phase 1, dose-escalation trial of PLX4032 (also known as RG7204), an orally available inhibitor of mutated BRAF, followed by an extension phase involving the maximum dose that could be administered without adverse effects (the recommended phase 2 dose). Patients received PLX4032 twice daily until they had disease progression. Pharmacokinetic analysis and tumor-response assessments were conducted in all patients. In selected patients, tumor biopsy was performed before and during treatment to validate BRAF inhibition.

RESULTS: A total of 55 patients (49 of whom had melanoma) were enrolled in the dose-escalation phase, and 32 additional patients with metastatic melanoma who had BRAF with the V600E mutation were enrolled in the extension phase. The recommended phase 2 dose was 960 mg twice daily, with increases in the dose limited by grade 2 or 3 rash, fatigue, and arthralgia. In the dose-escalation cohort, among the 16 patients with melanoma whose tumors carried the V600E BRAF mutation and who were receiving 240 mg or more of PLX4032 twice daily, 10 had a partial response and 1 had a complete response. Among the 32 patients in the extension cohort, 24 had a partial response and 2 had a complete response. The estimated median progression-free survival among all patients was more than 7 months.

CONCLUSIONS: Treatment of metastatic melanoma with PLX4032 in patients with tumors that carry the V600E BRAF mutation resulted in complete or partial tumor regression in the majority of patients. (Funded by Plexxikon and Roche Pharmaceuticals.)

of nce	Reference
	(Flaherty, 2010)
	(Chapman, 2011)
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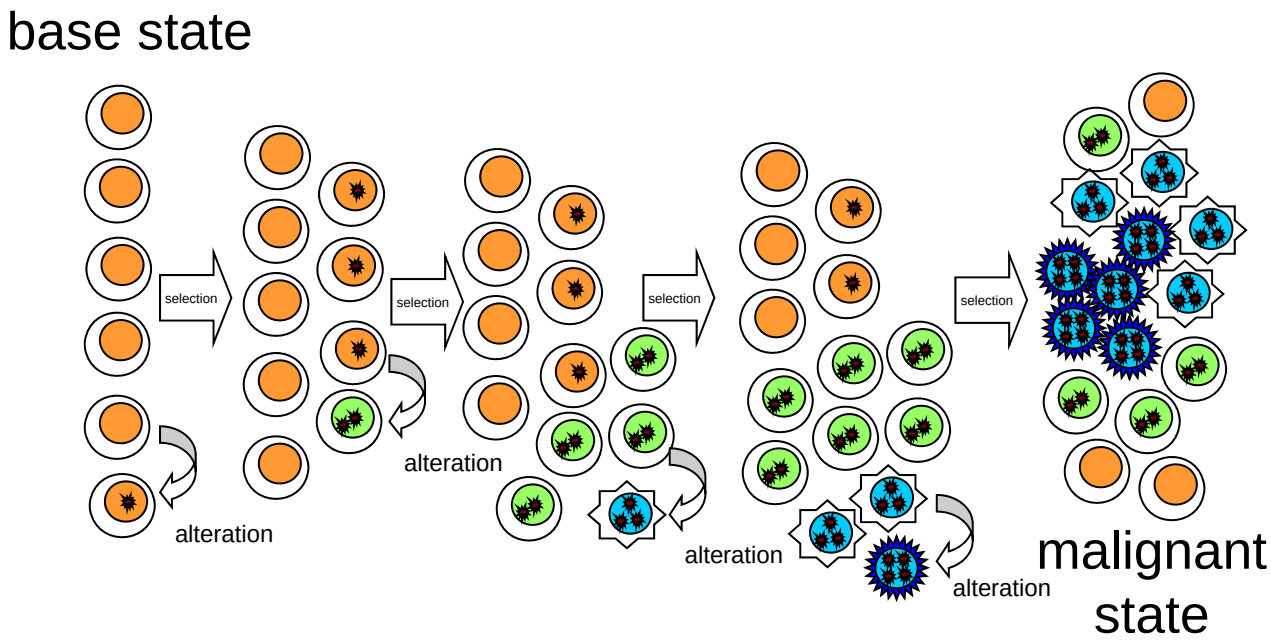
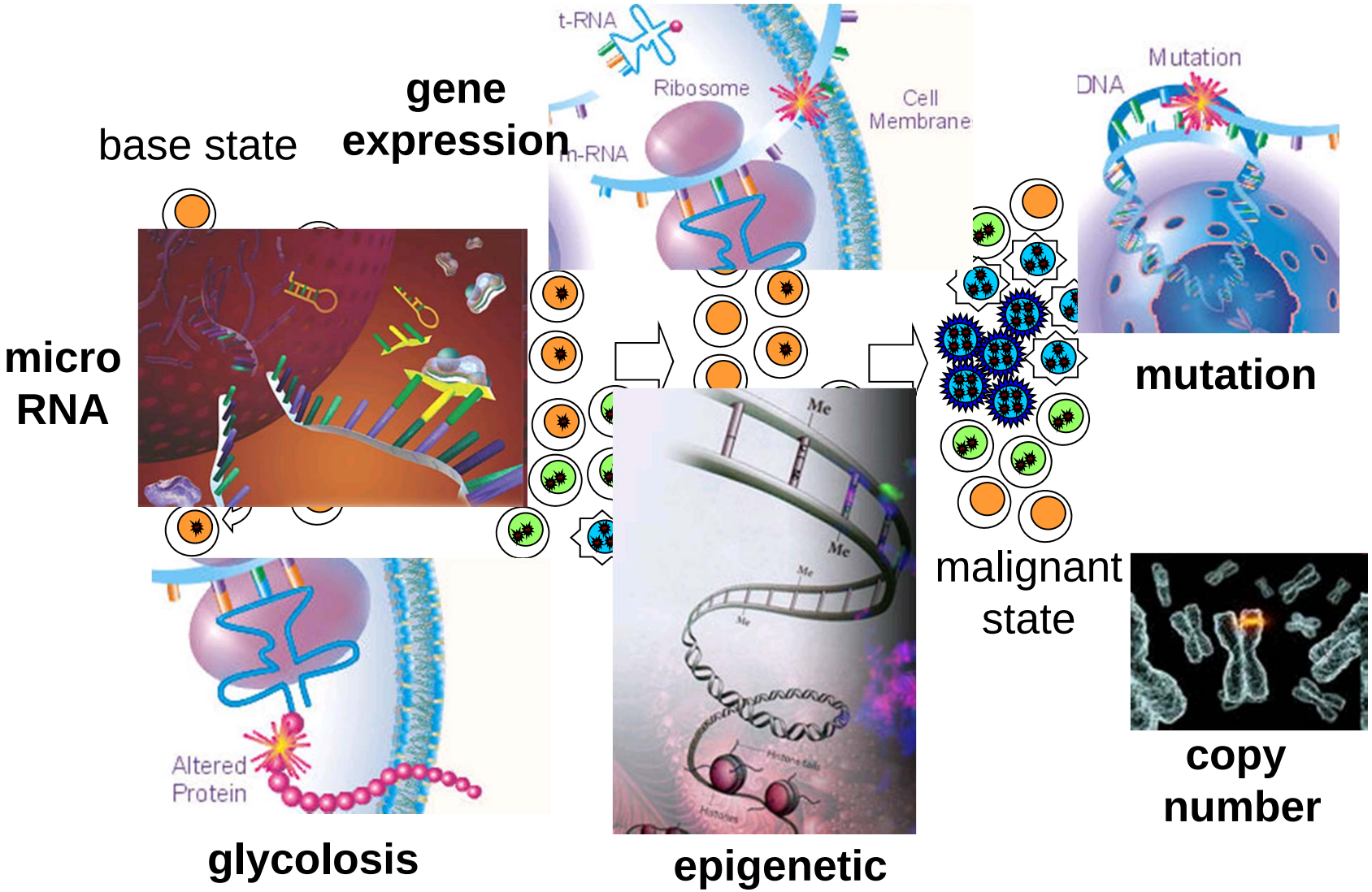
The Future
NEXT EXIT

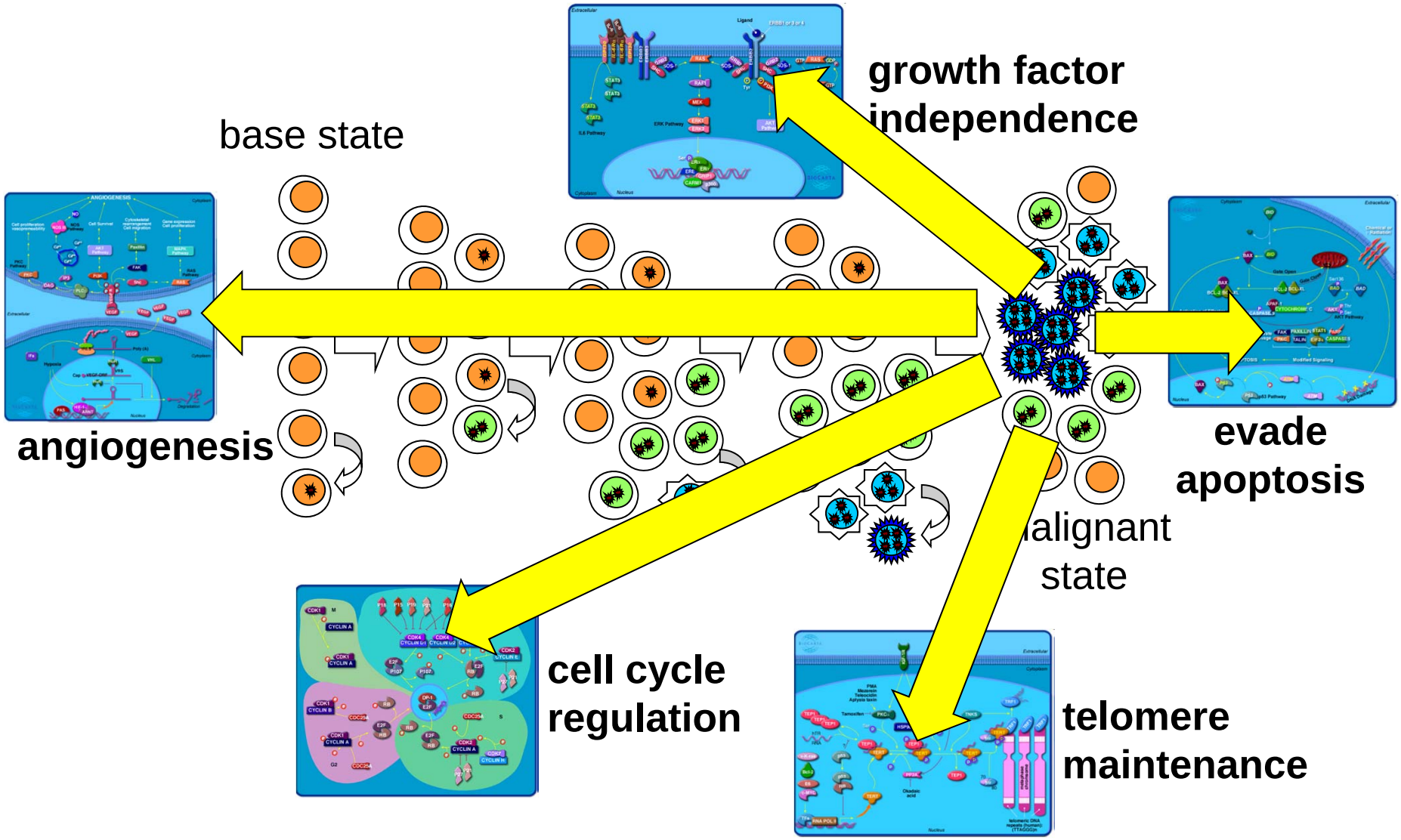
Cancer is a Complex Adaptive System



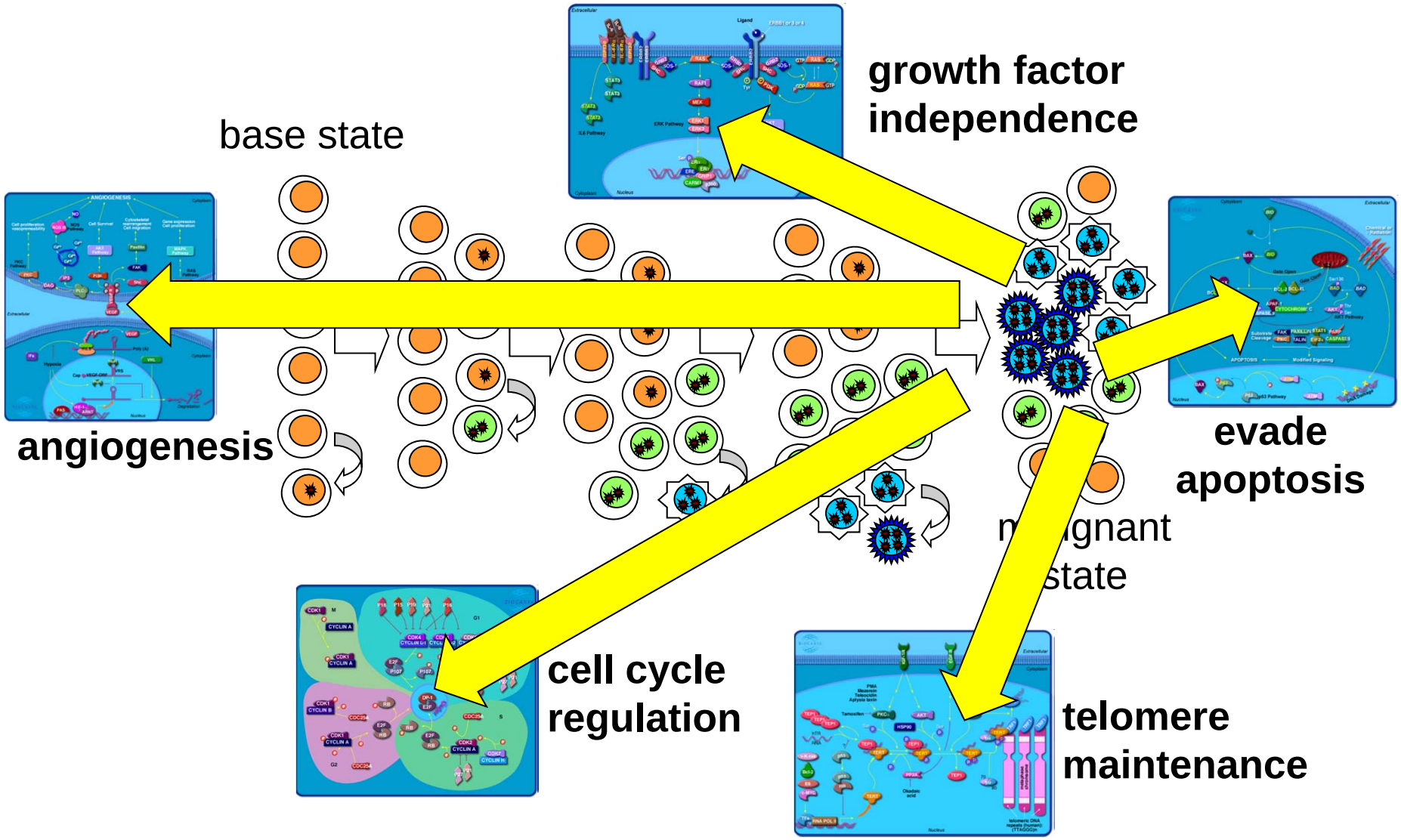
Cancer is a Complex Adaptive System



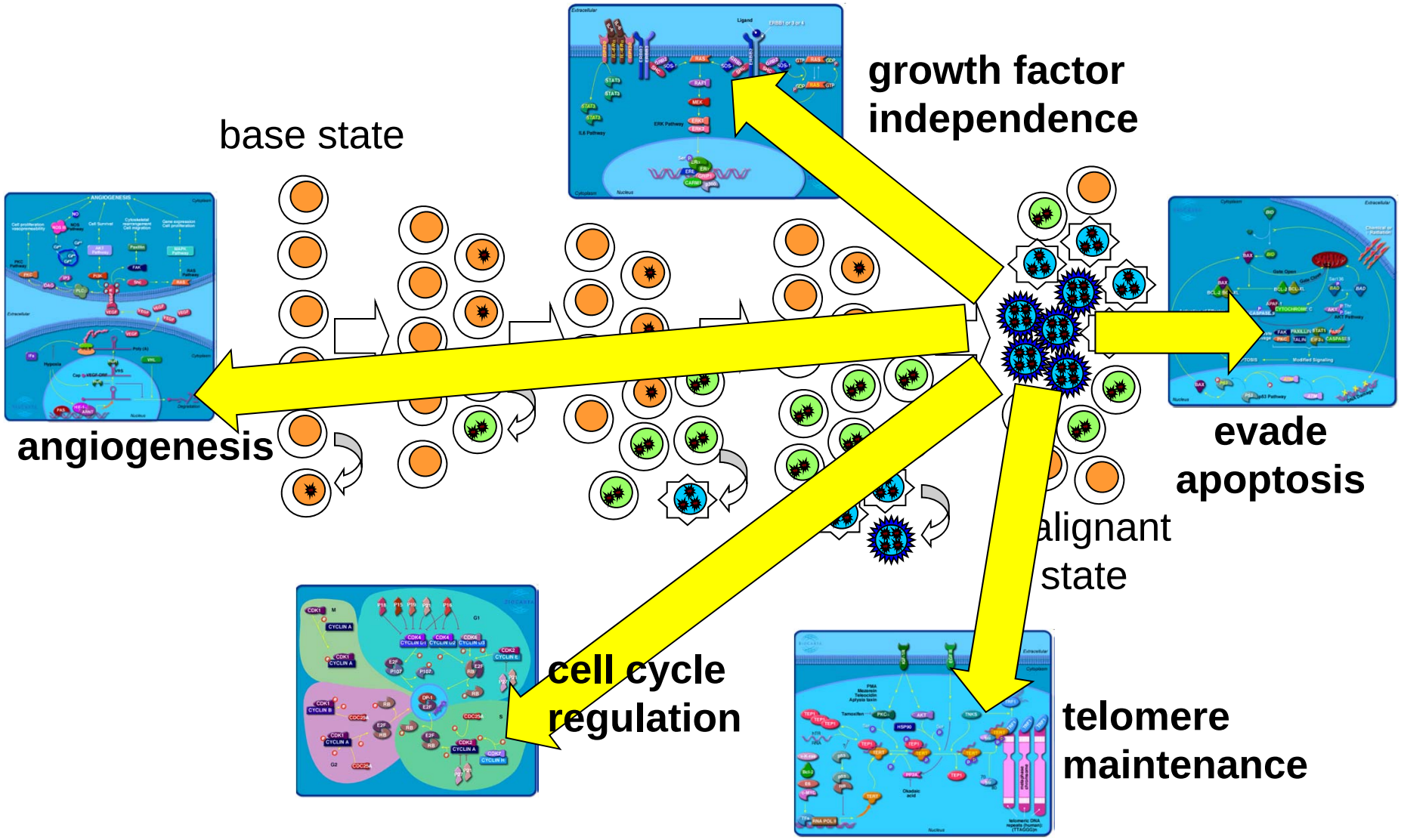
Cancer is a Complex Adaptive System



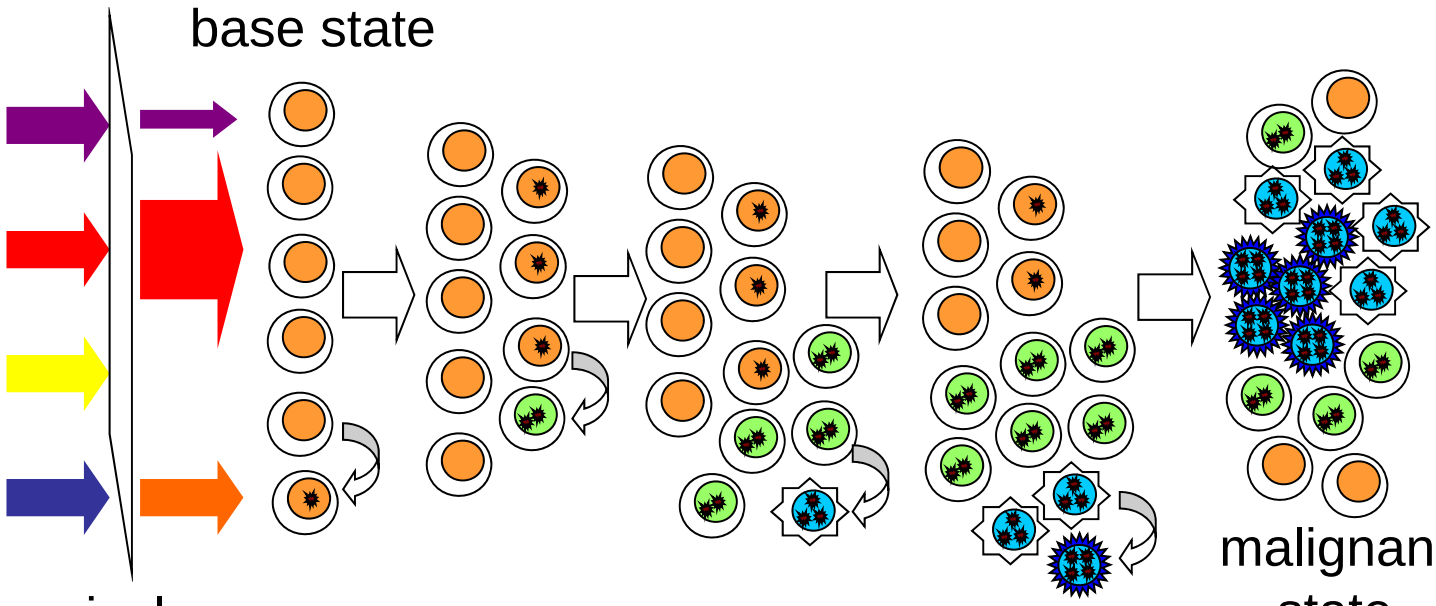
Cancer is a Complex Adaptive System



Cancer is a Complex Adaptive System

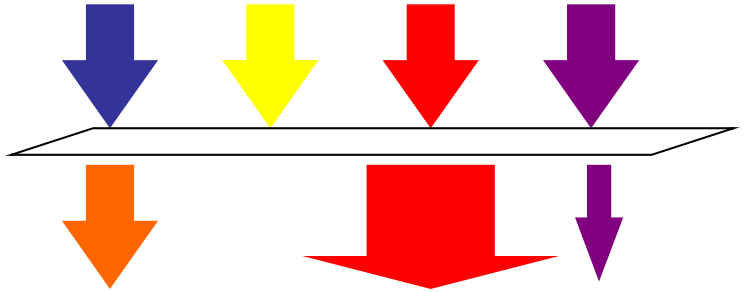


Cancer is a Complex Adaptive System



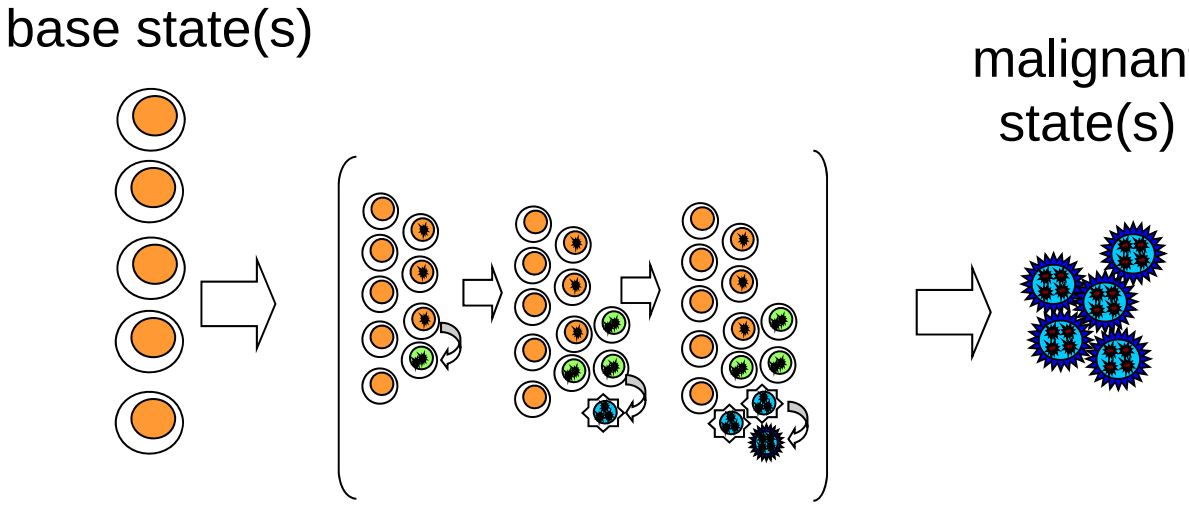
- chemical
- virus
- hormone
- nutrition

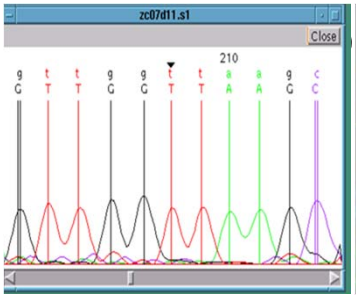
genetic constitution



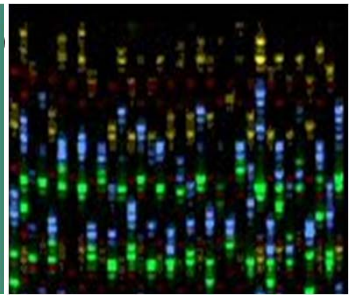
- angiogenesis
- cellular matrix
- immune response

Multiple systems technologies are needed to triangulate molecular state of disease

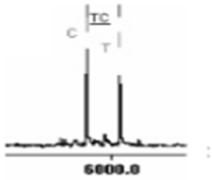




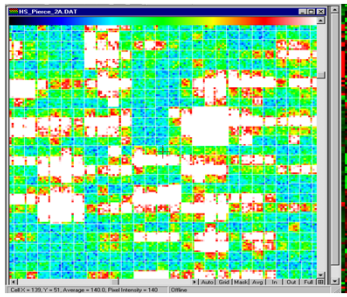
Mutation status



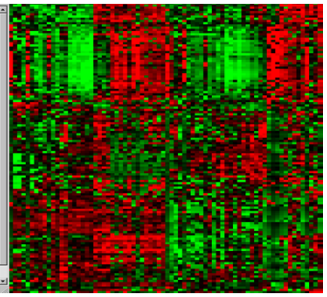
Allele loss



Constitutional variation

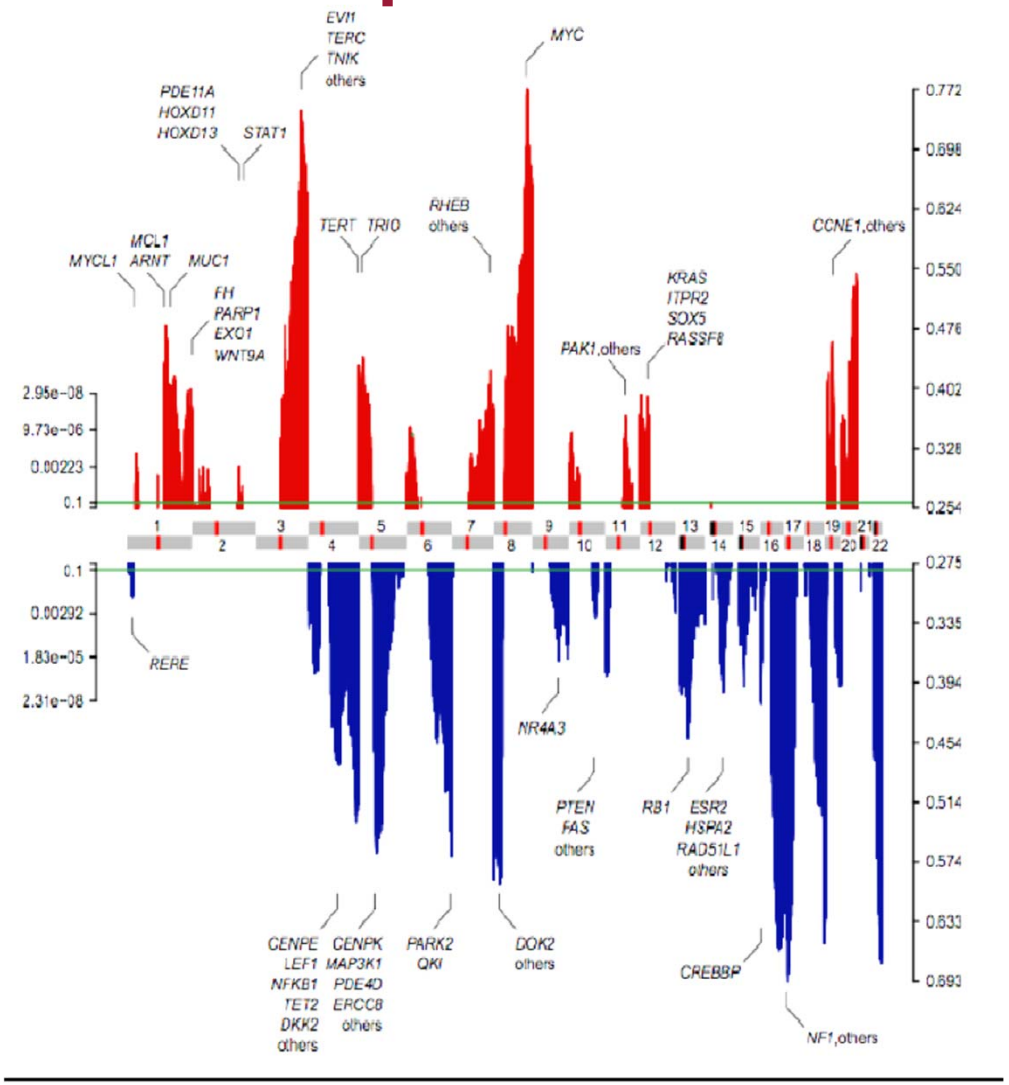


Epigenetic variation

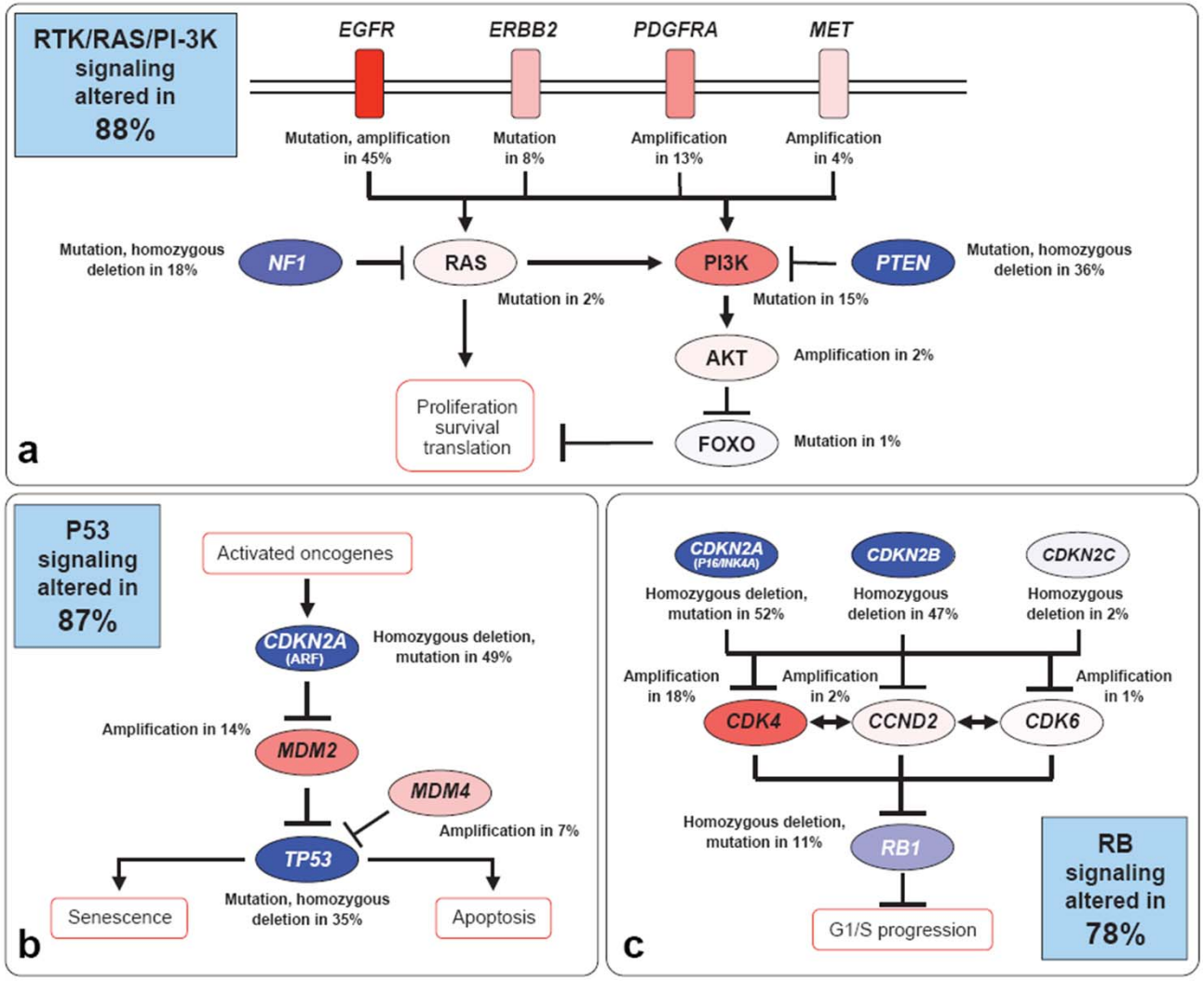


RNA expression

TCGA Ovarian Cancer
Chromosomal Amplifications and Deletions



TCGA Glioblastoma Multiforme



TCGA: *Nature* 2008

Patient selection for HER2 Tx required tissue screen and allowed only 1 of 4 women to participate

Calculated Sample Size And Study Duration	Hypothetical HER2+ Prevalence	Required "Screened" Population
1250 ➡ 52 mos	100%	1250
	50%	2500
	25%	5000

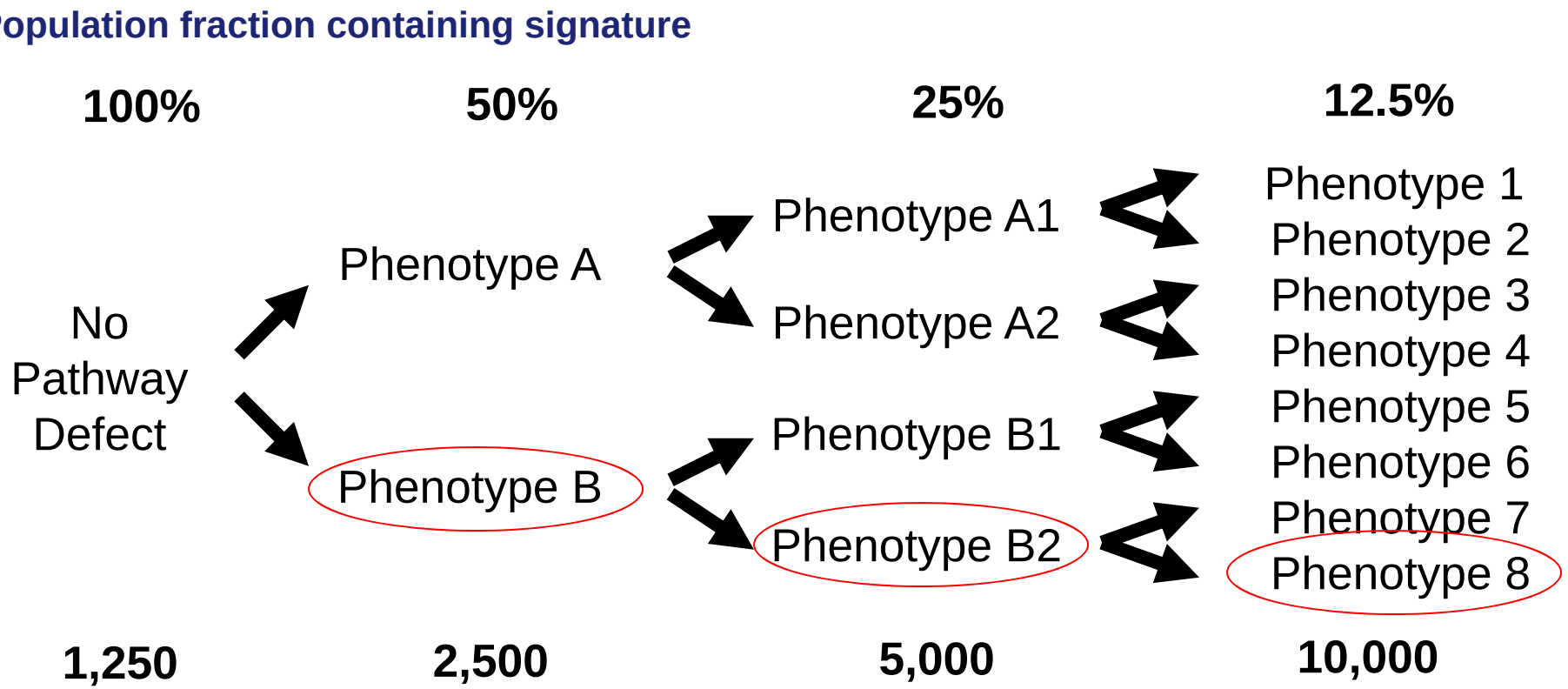
** Need a obtain a suitable specimen, wait for test results. (Results were obtained in days to weeks)*

** Need to screen many patients.*

Courtesy H. Kim Lyerly, M.D.,

Duke Comprehensive Cancer Center

Size of Population with “Pathway” to Inhibit



Courtesy H. Kim Lyerly, M.D.,

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Biomedicine: “fallen and I can’t get up”

- Impending “*Pharmageddon*”*: Declining R&D Productivity with Rising Costs
- Healthcare ecosystem is broken
- Poor understanding of the underlying biological complexity – current dominance of reductionist paradigm
- Vertically integrated development model (FIPCo) vs networked model (FIPNet) that dominates other sectors
- Exponential fragmentation of health information

need to embrace biomedicine as *SYSTEM*

* from M. King Jolly, Pharm.D. Quintiles, Inc. **DIA 2011**

Biomedicine: a Complex Adaptive System

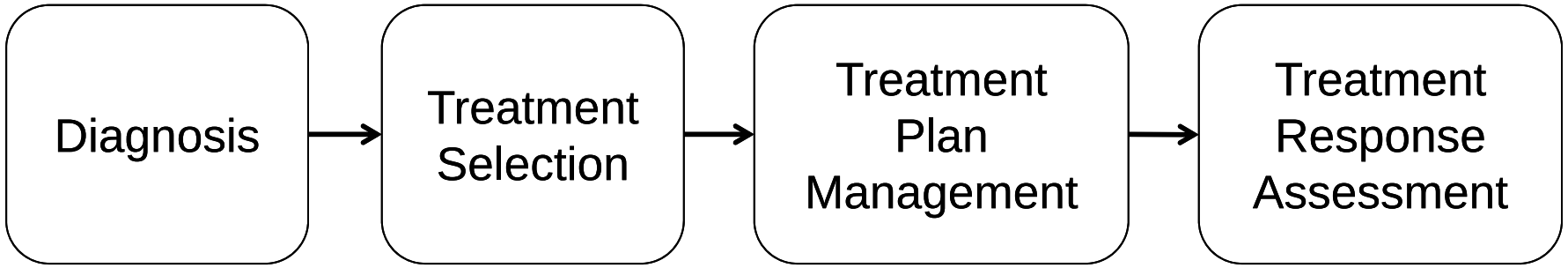
"the whole is more than the sum of the parts"

- Diverse stakeholders: multidimensional, interacting ***"ecosystem"***
  - Industry, Academe, Government, ***NGOs***
  - Physicians, Regulators, Researchers, ***Payors, Consumers, Public Health Officials***
  - Biology, Chemistry, Medicine, Business, ***Sociology, Anthropology***
- Adaptive behaviors (dynamic as opposed to static)
- Emergent properties (or unintended consequences)
- Interdependencies
  - Resourses
  - ***Information***

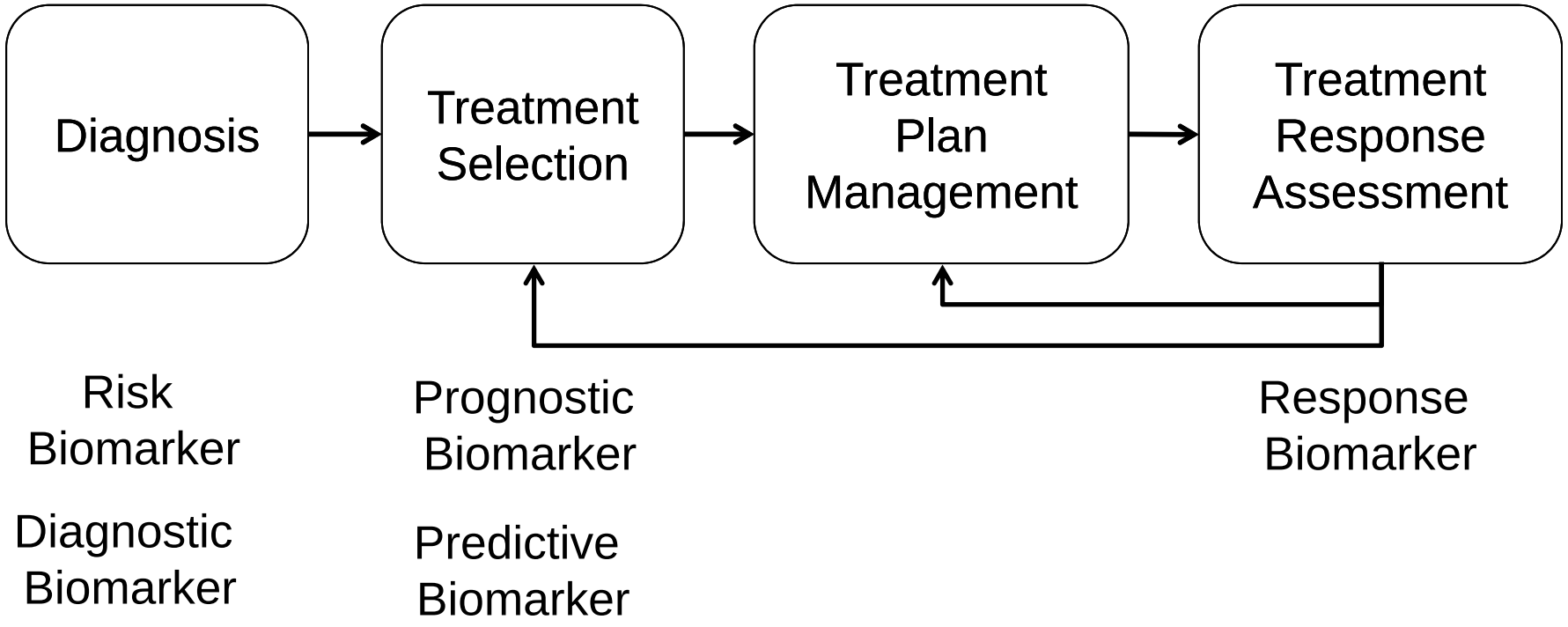
Strategies for "Managing" Complexity

- **Networking**
  - **Differentiated functions** connected though well-defined **interfaces** – e.g.
    - Biologic processes
    - Manufacturing
- **Layering**
  - **Abstracted combinations of functions** into hierarchical/multidimensional strata which connect through well defined **interfaces** –e.g.
    - Quantum physics – Newtonian physics
    - Biologic complexity : cell, organism, society
    - Organizational hierarchies

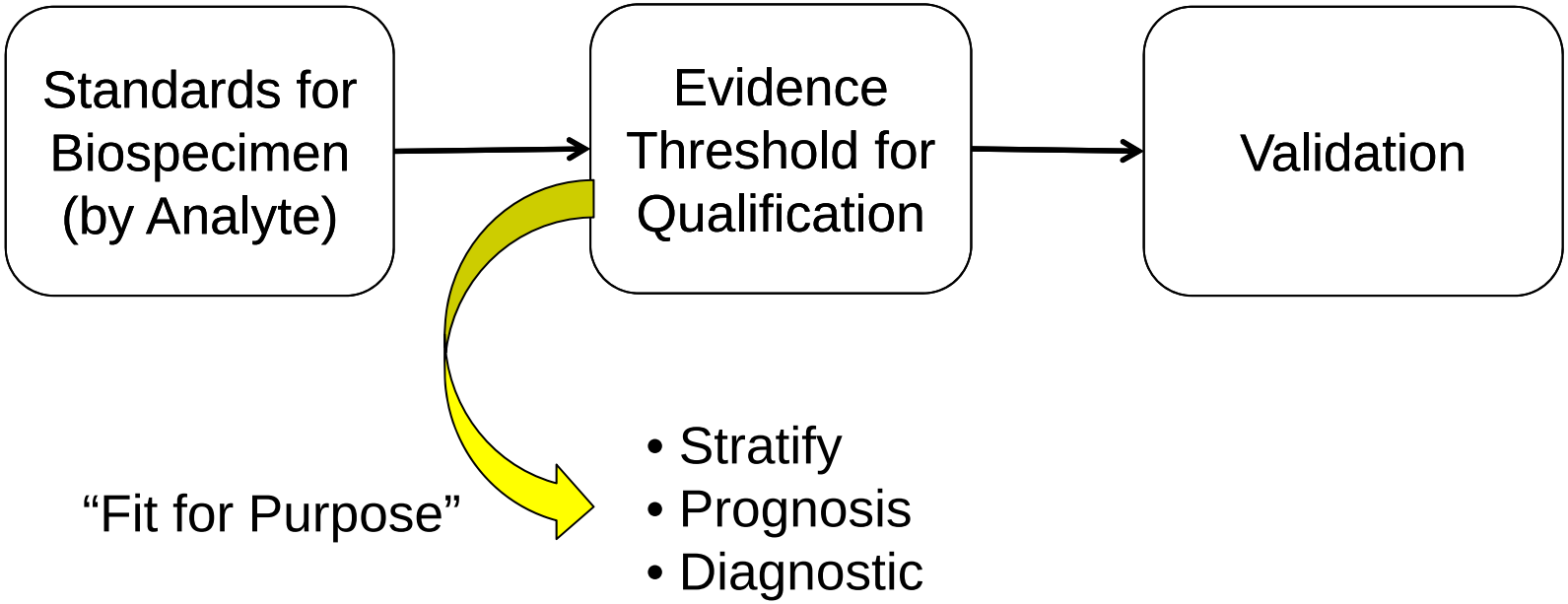
Clinical Continuum



Clinical Biomarkers

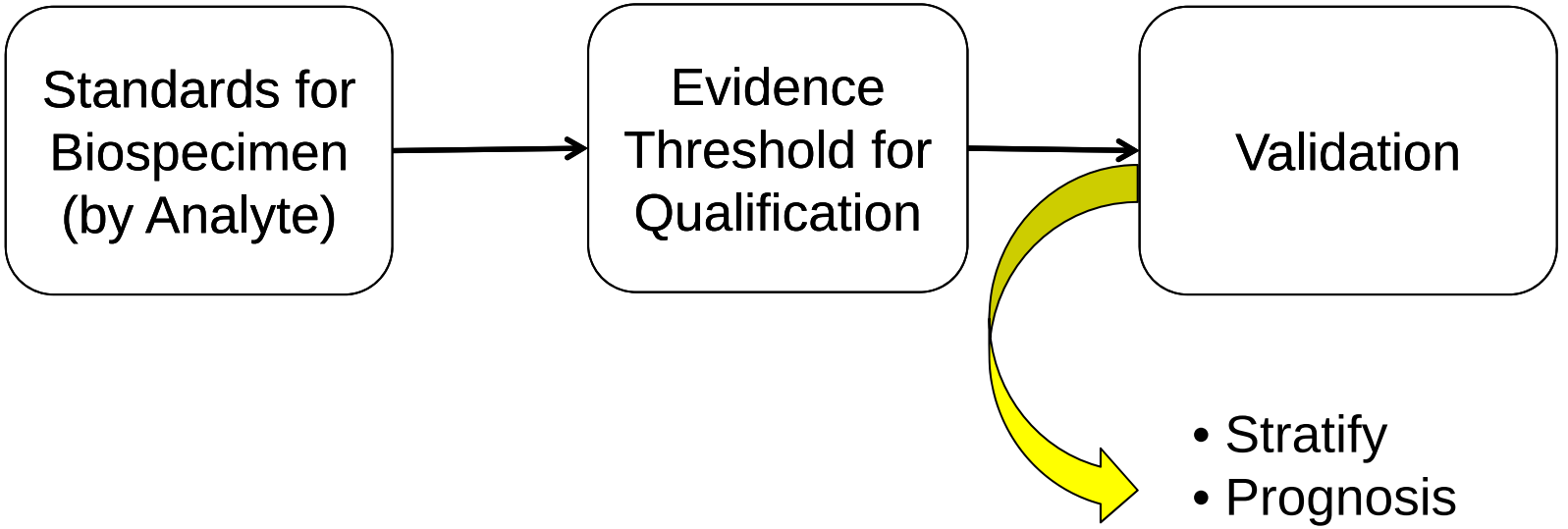


Evidence Generation “System”



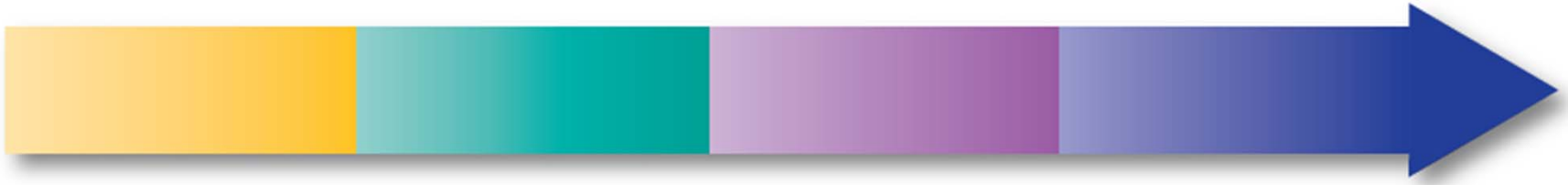
(each requires different evidence)

Evidence Generation “System”

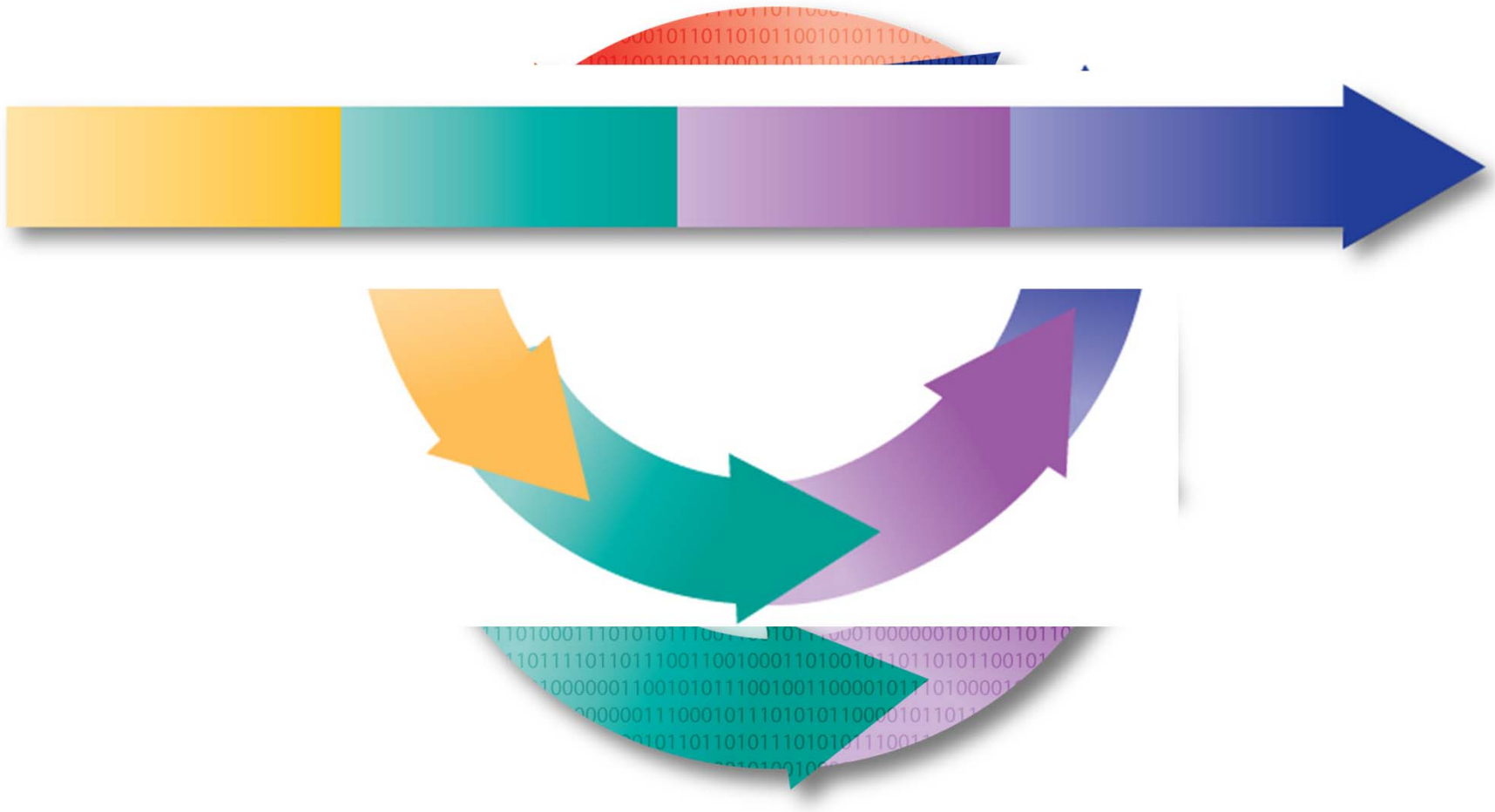


(different designs for each class)

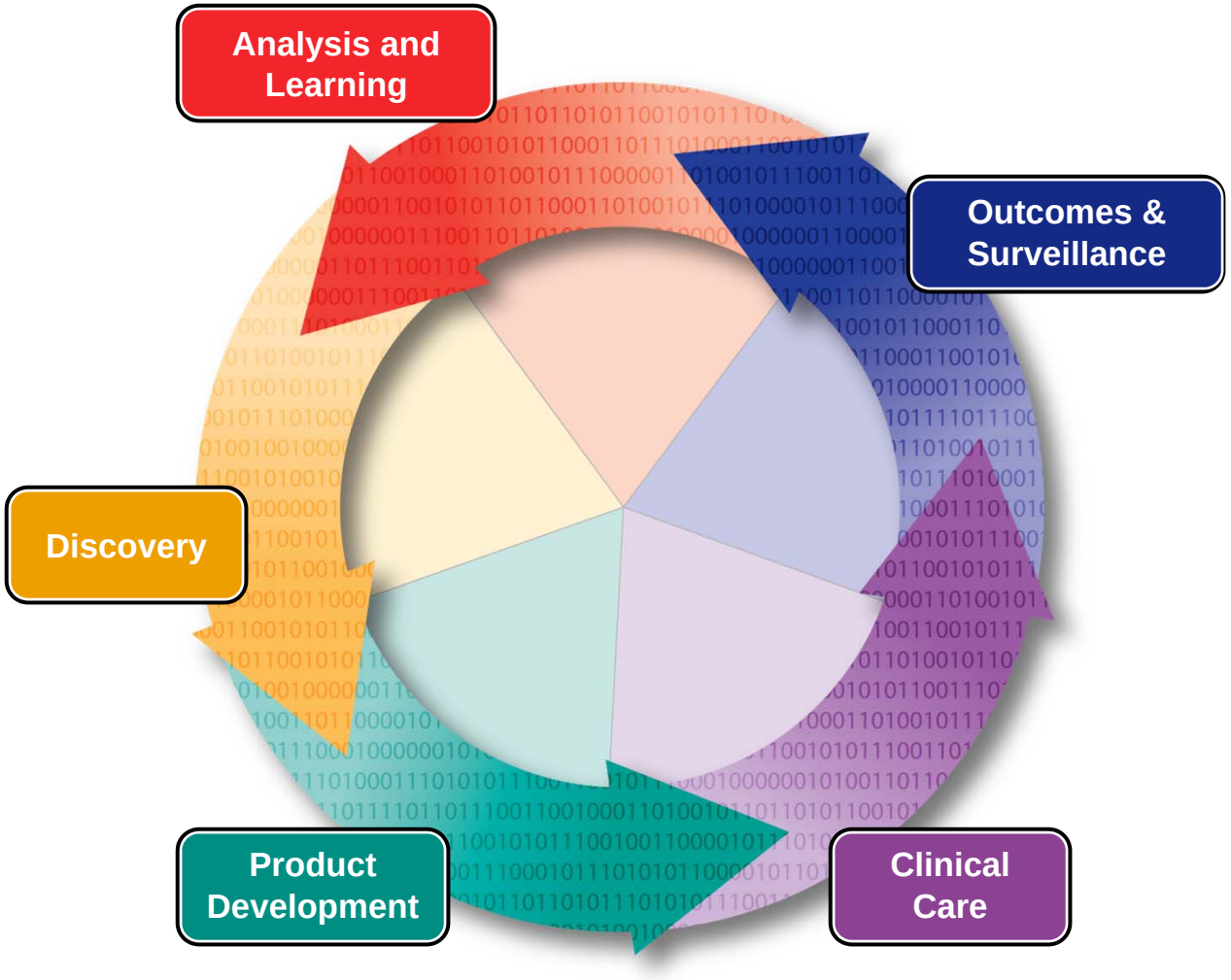
20th Century Research > Care Paradigm



Discovery	Product Development	Clinical Care	Outcomes & Surveillance
• Biological pathways • Target identification and validation	• Candidate selection and Optimization • Pre-clinical testing • Phase I, II, III • New Drug application and Approval	• Product launch • Clinical adoption	• Reporting of serious/fatal ADRs • Re-labeling (or recall) as needed • Additional indications as warranted



21st Century Learning Health System



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  - BRAF c.1798G>A (V600M)
  - BRAF c.1799T>G (V600G)
  - BRAF c.1799_1800TG>AT (V600D)
- CTNNB1
- GNA11
- GNAQ
- KIT
- NRAS

- Other Cancers

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BRAF V600E (c.1799T>A) mutation in Melanoma

What is BRAF? | BRAF in Melanoma | BRAF V600E mutation | Clinical Trials

BRAF c.1799T>A (V600E) mutation in Melanoma

BRAF V600E mutation	
Properties	
Location of mutation	Kinase domain (exon 15)
Frequency of BRAF V600E	~85-90% of BRAF mutant melanoma
Implications for Targeted Therapeutics	
Response to BRAF inhibitors	Confers increased sensitivity*
Response to MEK inhibitors	Uncertain at this time#
Response to KIT inhibitors	Uncertain at this time

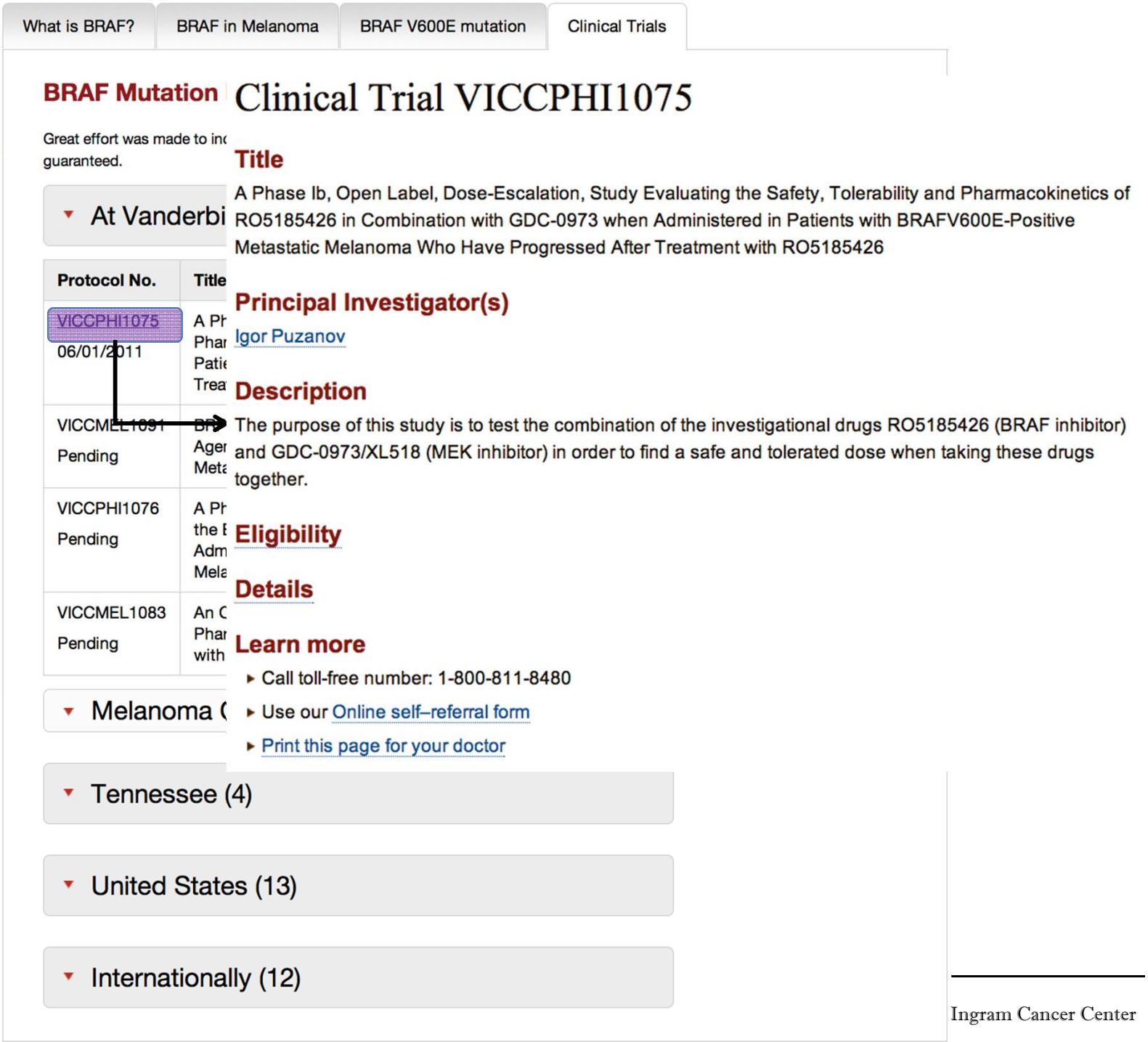
The V600E mutation results in an amino acid substitution at position 600 in BRAF, from a Valine (V) to a glutamic acid (E). This mutation occurs within the activation segment of the kinase domain **(Fig. 2)**. Approximately 70-90% of V600 BRAF mutations are V600E (Rubinstein, 2010). Mutant BRAF proteins have increased kinase activity and are transforming in vitro (Davies, 2002). BRAF mutations are usually found in tumors wildtype for NRAS, KIT, and other driver mutations.

Figure 2: Schematic of BRAF V600E mutation. Functional domains of BRAF are depicted. CR1: conserved regions 1. CR2: conserved region 2.

*In the initial phase I trial, patients with metastatic melanoma whose tumor harbored a BRAF V600E mutation displayed an 81% response rate to vemurafenib (PLX4032), an orally available inhibitor of mutated BRAF. The estimated progression-free survival was > 7 months and overall survival had not been reached at the time of study publication (Flaherty, 2010). In the follow-up randomized phase III trial comparing vemurafenib to dacarbazine in previously untreated, metastatic melanoma with the BRAF V600E mutation, vemurafenib improved rates of overall survival and progression-free survival (Chapman, 2011).

#Pre-clinical data has correlated the presence of activating mutations in BRAF with sensitivity to non-ATP competitive MEK inhibitors, AZD6244 and CI-1040 (Davies, 2007; Solit, 2006). In a Phase II clinical trial of AZD6244 versus temozolomide, 5 of 42 melanoma patients with BRAF V600E mutation had confirmed partial responses (12% objective response rate) (Dummer, 2008).

BRAF V600E mutation								
Treatment Agent	Drug Class	Line of Treatment	# pts in study	Response Rate	PFS (months)	OS (months)	Level of evidence	Reference
vemurafenib (PLX4032)	Mutated BRAF TKI^	1st to >3rd	32^	81%	> 7 months (estimated)	Not reached	II-1	(Flaherty, 2010)
vemurafenib (PLX4032)	Mutated BRAF TKI^	1st	337	48%	5.3	84% at 6 mos	I	(Chapman, 2011)
dacarbazine	Cytotoxic chemotherapy	1st	338	5%	1.6	64% at 6 mos	I	(Chapman, 2011)


What is BRAF?
BRAF in Melanoma
BRAF V600E mutation
Clinical Trials
BRAF Mutation
Great effort was made to inc
guaranteed.
At Vanderbi
Protocol No.
Title
VICCPHI1075
06/01/2011
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Tennessee (4)
United States (13)
Internationally (12)
Clinical Trial VICCPHI1075
Title
A Phase Ib, Open Label, Dose-Escalation, Study Evaluating the Safety, Tolerability and Pharmacokinetics of RO5185426 in Combination with GDC-0973 when Administered in Patients with BRAFV600E-Positive Metastatic Melanoma Who Have Progressed After Treatment with RO5185426
Principal Investigator(s)
Igor Puzanov
Description
The purpose of this study is to test the combination of the investigational drugs RO5185426 (BRAF inhibitor) and GDC-0973/XL518 (MEK inhibitor) in order to find a safe and tolerated dose when taking these drugs together.
Eligibility
Details
Learn more
Call toll-free number: 1-800-811-8480
Use our Online self–referral form
Print this page for your doctor

What is BRAF? | BRAF in Melanoma | BRAF V600E mutation | Clinical Trials

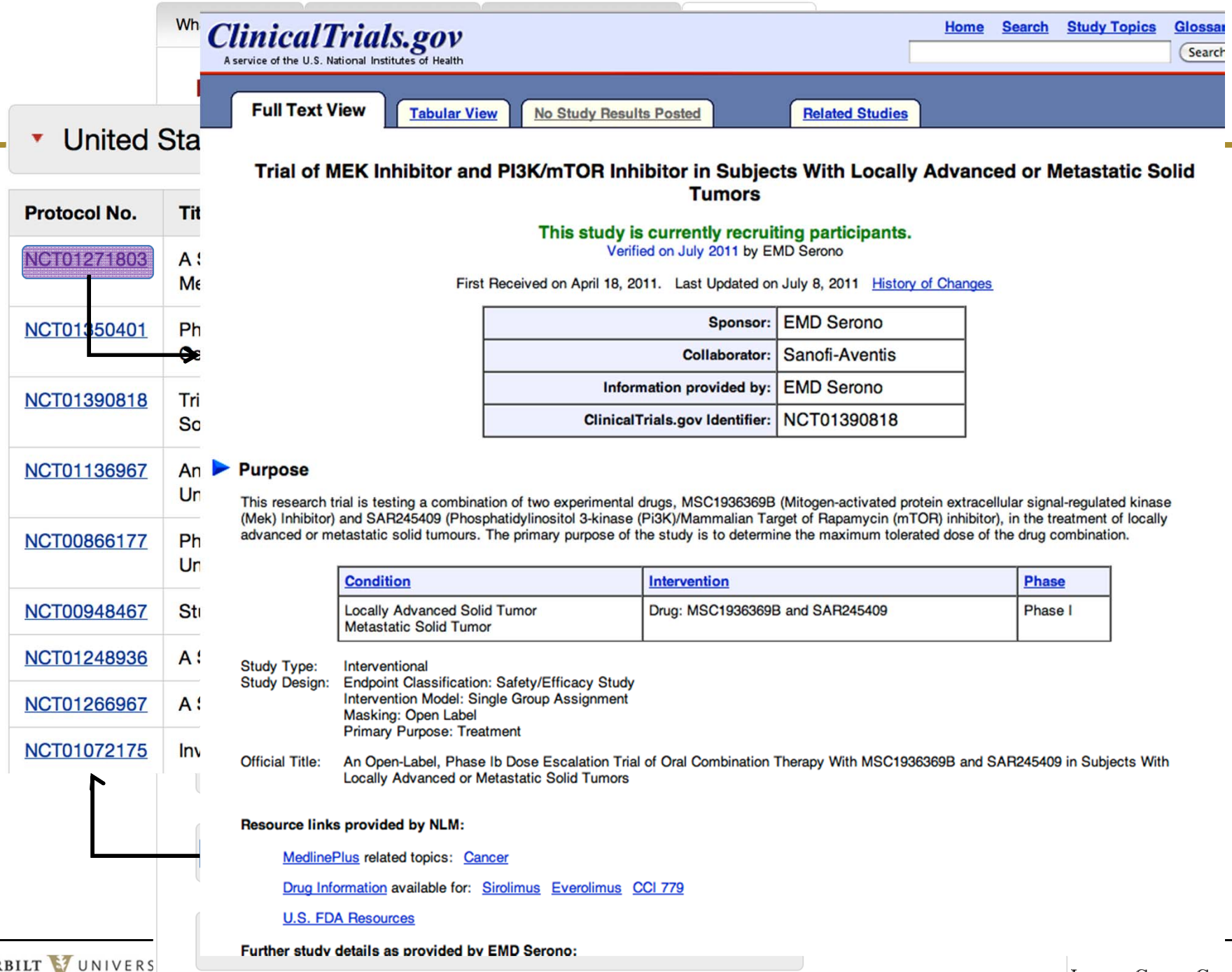
BRAF Mutation Directed Melanoma Clinical Trials

United States (13)

Protocol No.	Title
NCT01271803	A Study of RO5185426 And GDC-0973 in Patients With BRAF-Mutation Positive Metastatic Melanoma
NCT01350401	Phase I/II Study to Assess the Safety and Activity of Enhanced TCR Transduced Autologous T Cells in Metastatic Melanoma
NCT01390818	Trial of MEK Inhibitor and PI3K/mTOR Inhibitor in Subjects With Locally Advanced or Metastatic Solid Tumors
NCT01136967	An Open-Label, 2-Cohort, Multicenter, Study of E7080 in Previously Treated Subjects With Unresectable Stage III or Stage IV Melanoma
NCT00866177	Phase II Study of MEK Inhibitor AZD6244 in Patients With BRAF-Mutated or NRAS-Mutated, Unresectable Stage III or IV Melanoma
NCT00948467	Study of TAK-733 in Adult Patients With Advanced Nonhematologic Malignancies
NCT01248936	A Study of RO5185426 in Patients With Metastatic Melanoma
NCT01266967	A Study of GSK2118436 in BRAF Mutant Metastatic Melanoma to the Brain
NCT01072175	Investigate Safety, Pharmacokinetics and Pharmacodynamics of GSK2118436 & GSK1120212

United States (13)

Internationally (12)



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Protocol No.	Tit
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NCT01390818	Tri Sc
NCT01136967	An Ur
NCT00866177	Ph Ur
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NCT01248936	A S
NCT01266967	A S
NCT01072175	Inv

ClinicalTrials.gov
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Trial of MEK Inhibitor and PI3K/mTOR Inhibitor in Subjects With Locally Advanced or Metastatic Solid Tumors

This study is currently recruiting participants.
Verified on July 2011 by EMD Serono

First Received on April 18, 2011. Last Updated on July 8, 2011 History of Changes

Sponsor:	EMD Serono
Collaborator:	Sanofi-Aventis
Information provided by:	EMD Serono
ClinicalTrials.gov Identifier:	NCT01390818

Purpose

This research trial is testing a combination of two experimental drugs, MSC1936369B (Mitogen-activated protein extracellular signal-regulated kinase (Mek) Inhibitor) and SAR245409 (Phosphatidylinositol 3-kinase (Pi3K)/Mammalian Target of Rapamycin (mTOR) inhibitor), in the treatment of locally advanced or metastatic solid tumours. The primary purpose of the study is to determine the maximum tolerated dose of the drug combination.

Condition	Intervention	Phase
Locally Advanced Solid Tumor Metastatic Solid Tumor	Drug: MSC1936369B and SAR245409	Phase I

Study Type: Interventional
Study Design: Endpoint Classification: Safety/Efficacy Study
Intervention Model: Single Group Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: An Open-Label, Phase Ib Dose Escalation Trial of Oral Combination Therapy With MSC1936369B and SAR245409 in Subjects With Locally Advanced or Metastatic Solid Tumors

Resource links provided by NLM:

MedlinePlus related topics: Cancer

Drug Information available for: Sirolimus Everolimus CCI 779

U.S. FDA Resources

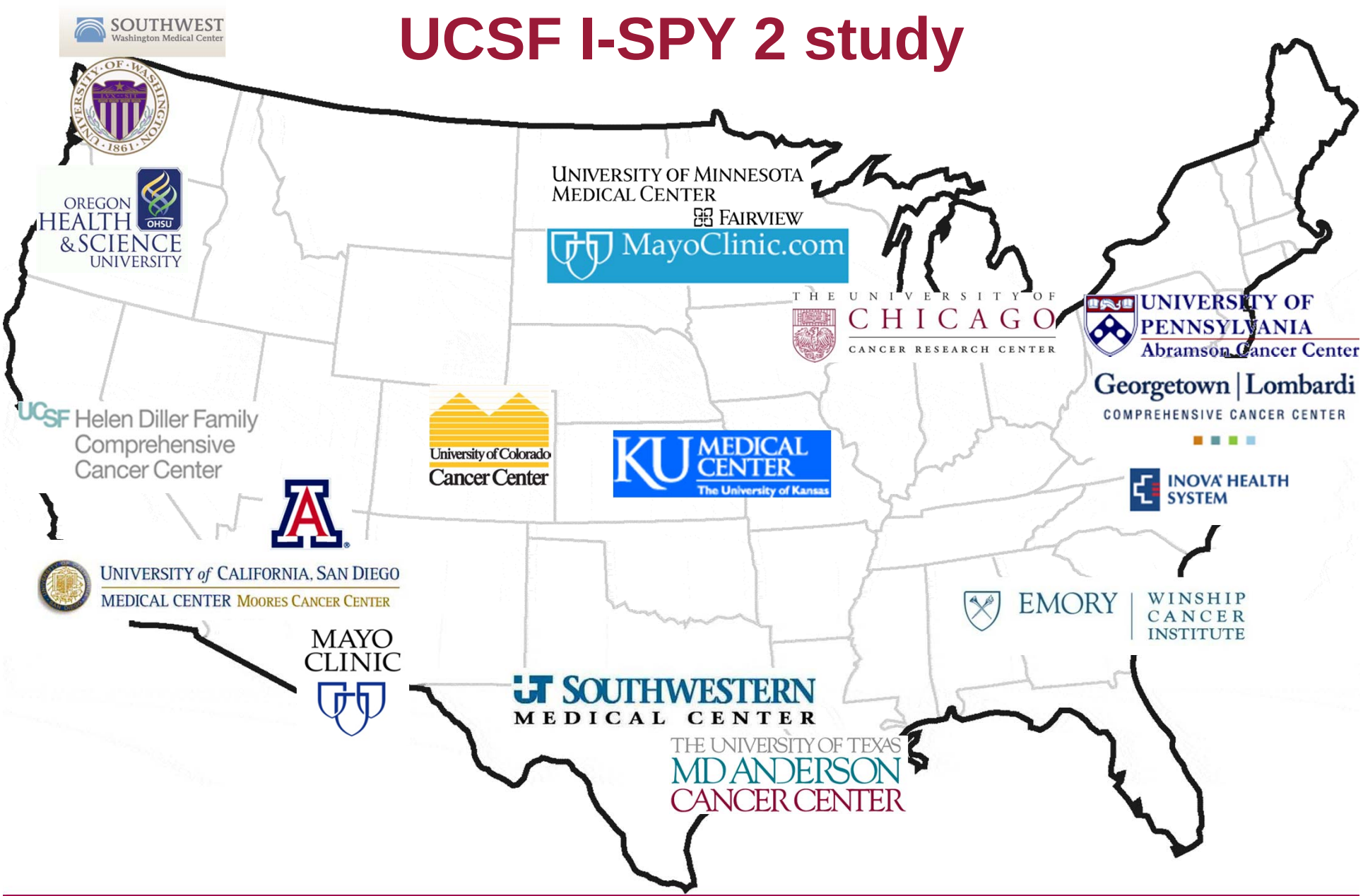
Further study details as provided by EMD Serono:

The I-SPY TRIAL (Investigation of Serial studies to Predict Your Therapeutic Response with Imaging And moLecular analysis):

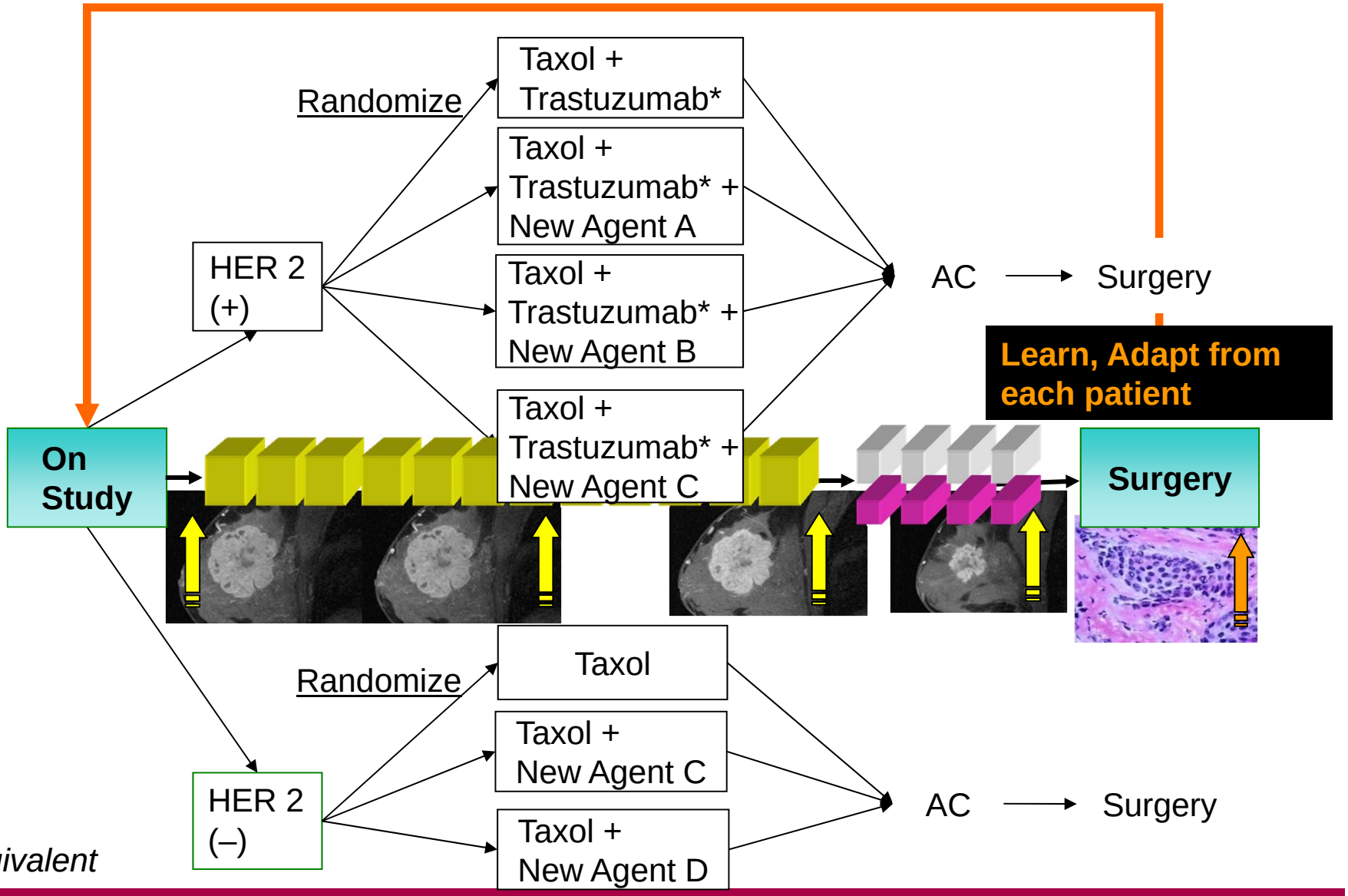
A national study to leverage biomarkers
in predicting response to combinatorial therapy for
women with Stage 3 breast cancer.

(PI Laura Esserman, UCSF)

UCSF I-SPY 2 study

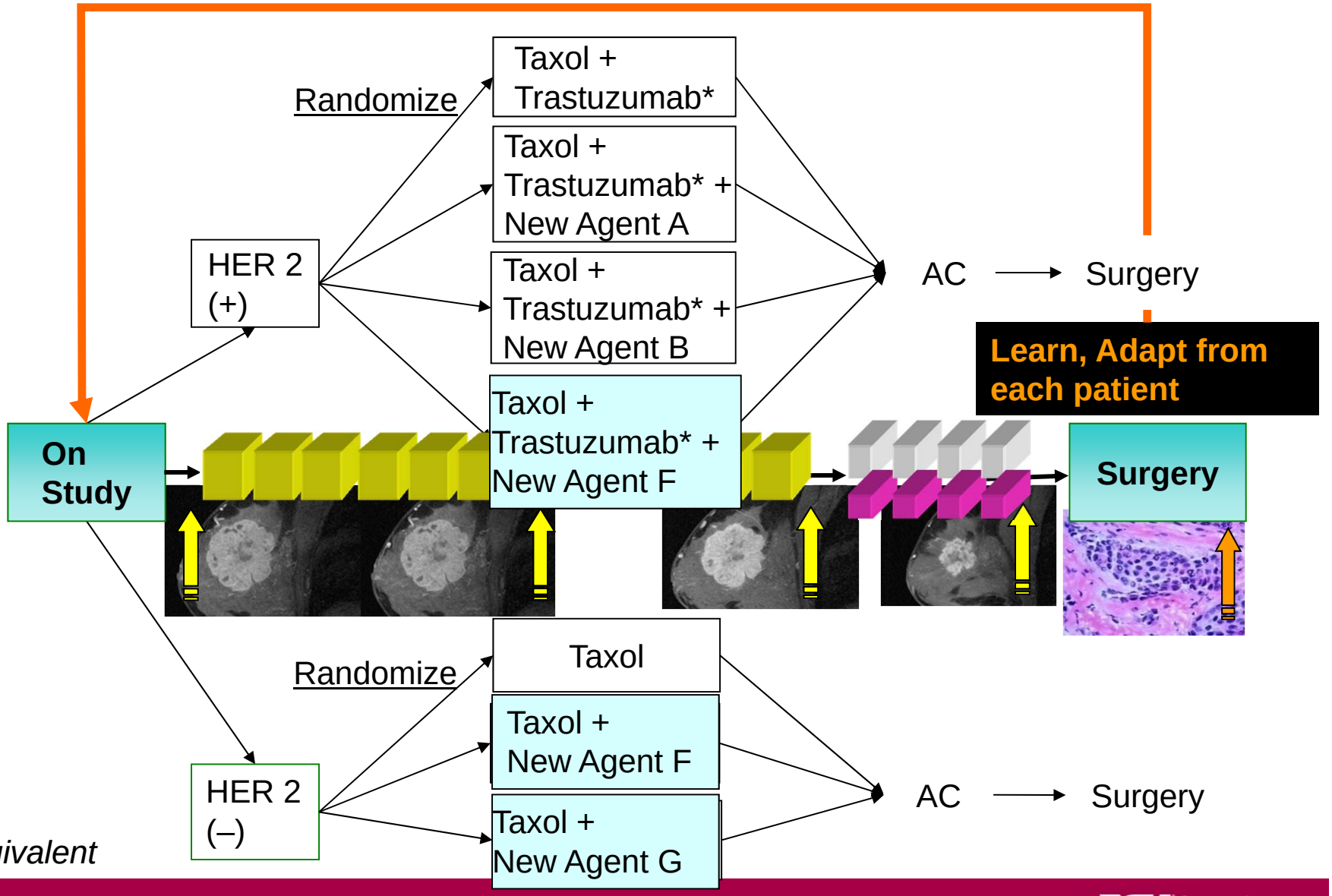


I-SPY Adaptive Trial:
Introduce several new agents for a given profile



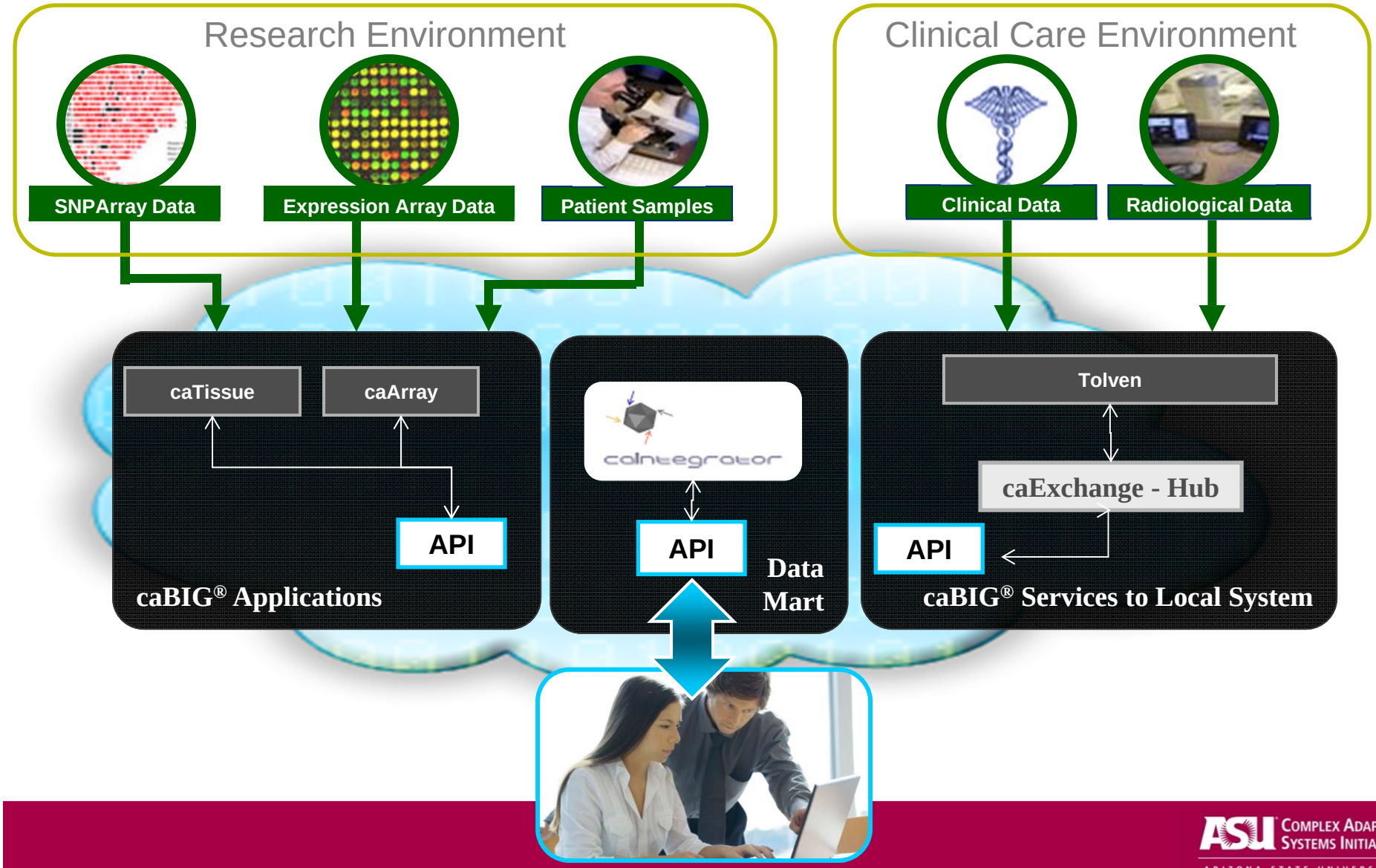
**Or Equivalent*

I-SPY Adaptive Trial:
Introduce several new agents for a given profile



**Or Equivalent*

I-SPY TRIAL IT Infrastructure



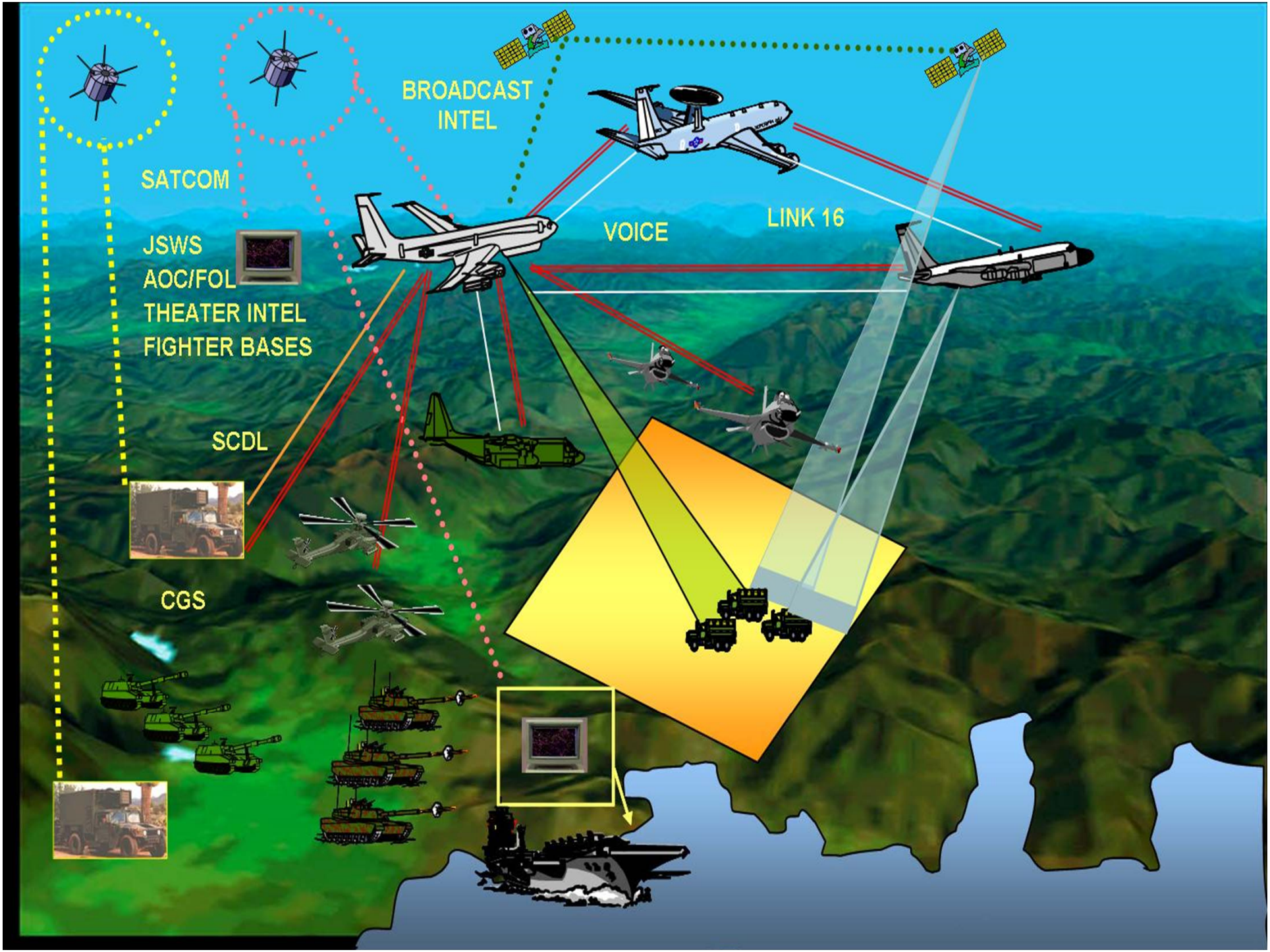
Network-centric “warfare”

A **military doctrine or theory of war pioneered by the United States Department of Defense**. It seeks to translate an information advantage, enabled in part by information technology, into a competitive warfighting advantage through the **robust networking** of **well informed geographically dispersed forces**. This networking, combined with changes in technology, organization, processes, and people - may allow new forms of organizational behavior.

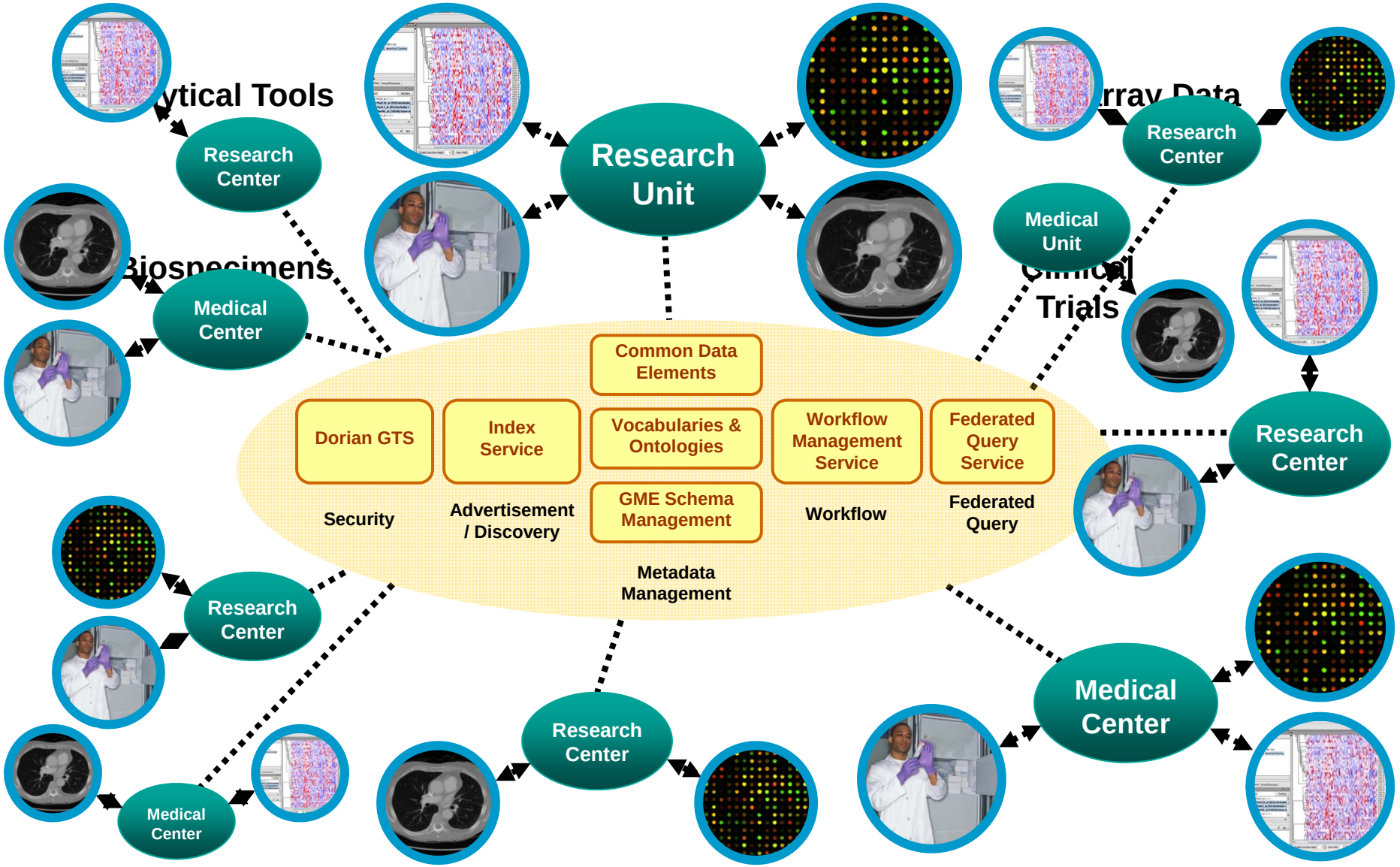
Specifically, the theory contains the following four tenets in its hypotheses:

- A robustly networked force **improves information sharing;**
- Information sharing **enhances the quality of information** and shared situational awareness;
- Shared situational awareness **enables collaboration** and **self-synchronization,** and **enhances sustainability** and speed of command; and
- These, in turn, dramatically **increase mission effectiveness.**

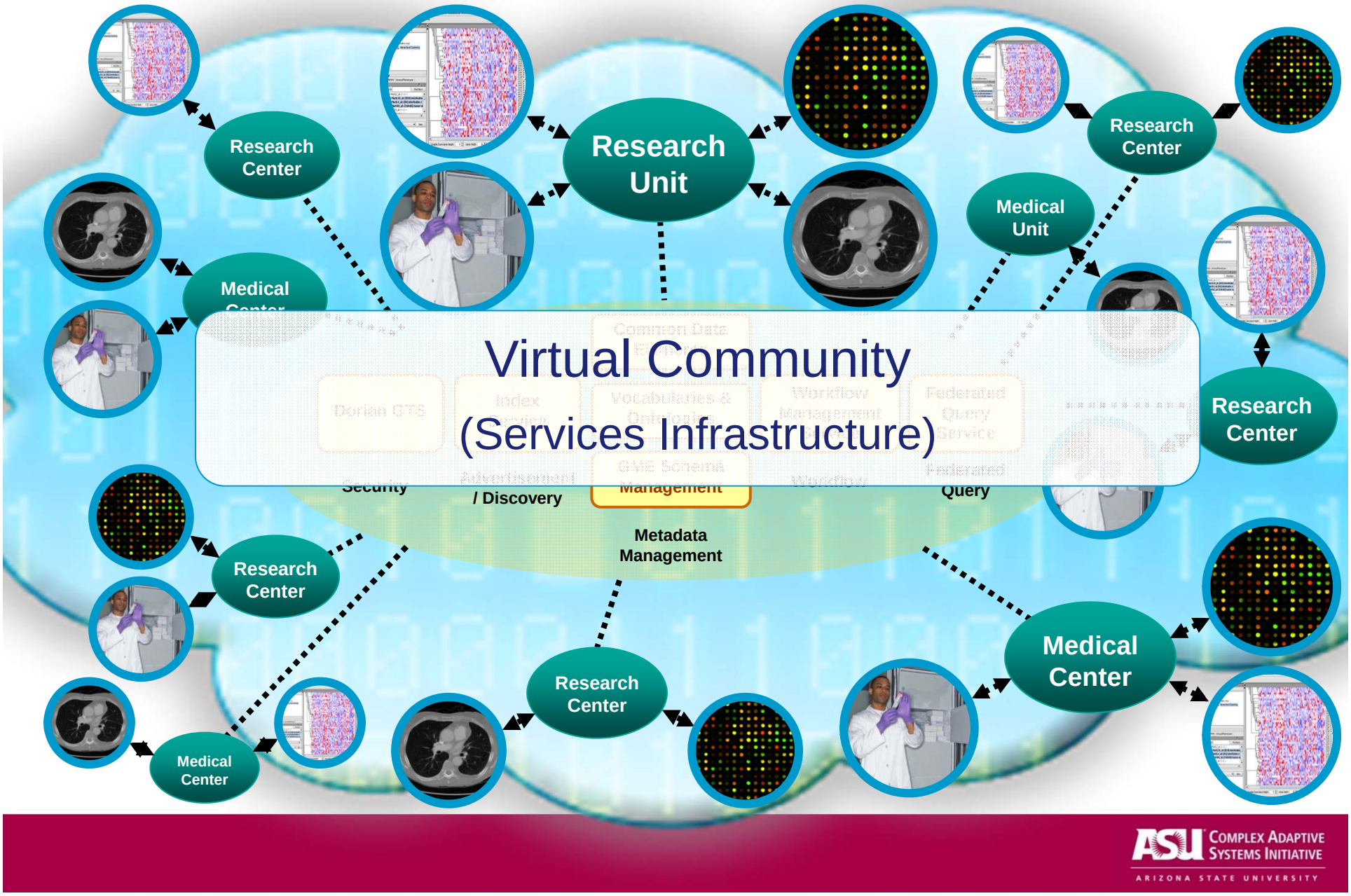
(Wikipedia)


BROADCAST
INTEL
SATCOM
JSWS
AOC/FOL
THEATER INTEL
FIGHTER BASES
VOICE
LINK 16
SCDL
CGS

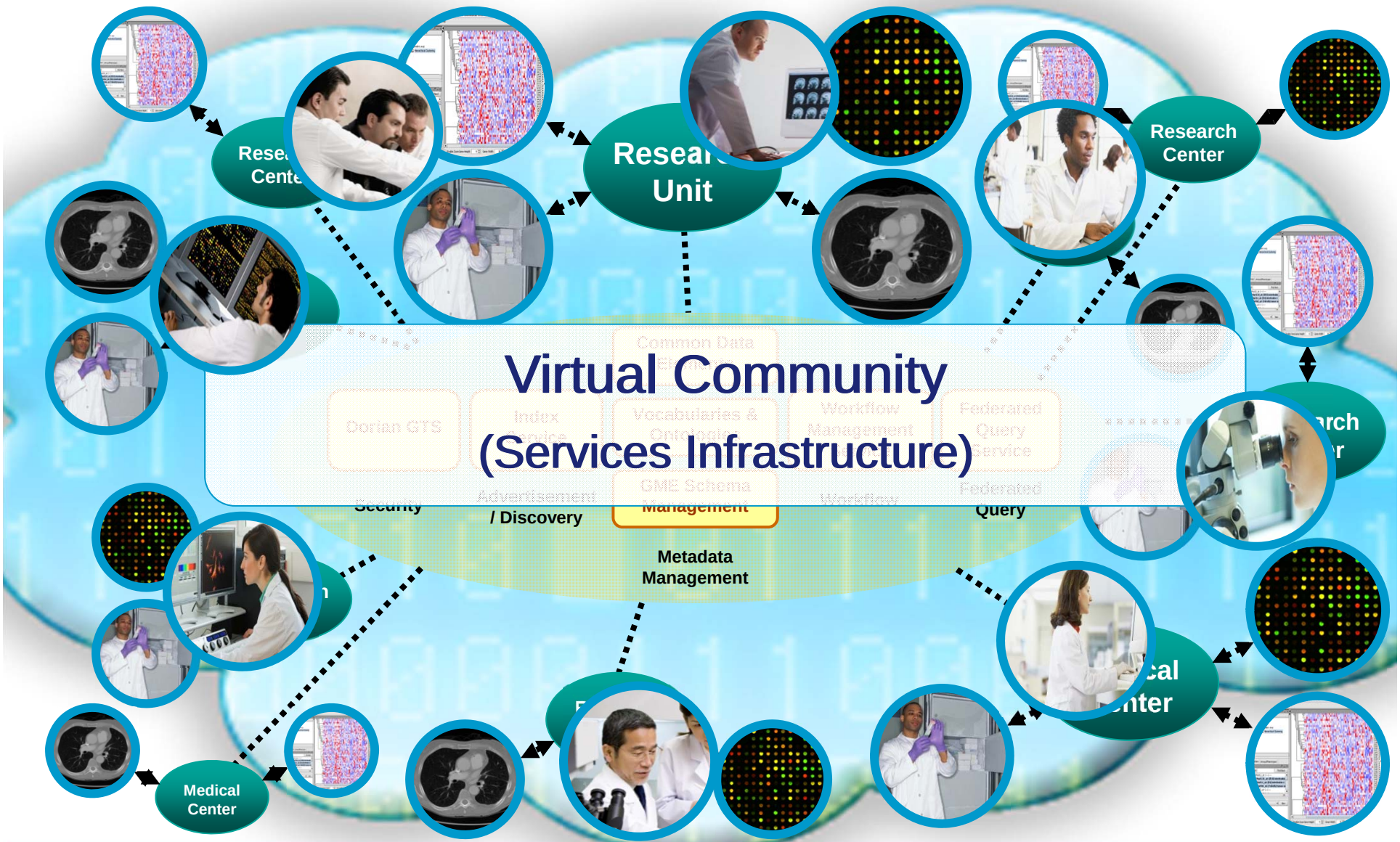
“Network-centric” Biomedicine



“Network-centric” Biomedicine



“Network-centric” Biomedicine



Summary

- The **future is already here** for biomarker-based biomedicine
- The biomedical **ecosystem is ill prepared** to address the **complexity** of common diseases such as cancer
- Approaching **biomedicine as a Complex Adaptive System** may help address some of the challenges it currently faces
- It is **technically feasible** to create and deploy technology to exchange information within and between members of the ecosystem
- A **multi-stakeholder, multidimensional community** will be necessary to create a sustainable ecosystem