Clinical decision support in the era of genome informed cancer medicine

Mia Levy, MD, PhD

Ingram Assistant Professor of Cancer Research

Director Cancer Health Informatics and Strategy

Assistant Professor of Biomedical Informatics

Assistant Professor of Medicine, Division of Hematology and Oncology

Vanderbilt University

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Personalis **Genomoncology**
Advisory Board fee **Consultant fee**
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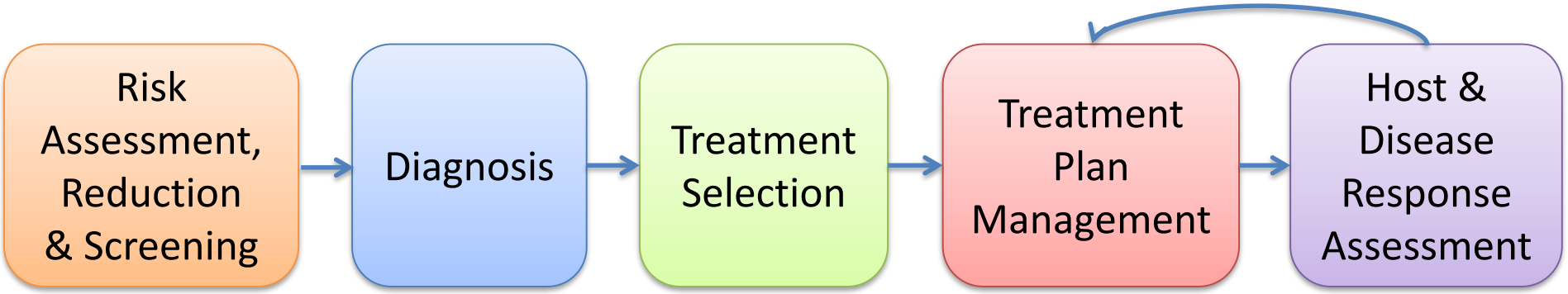
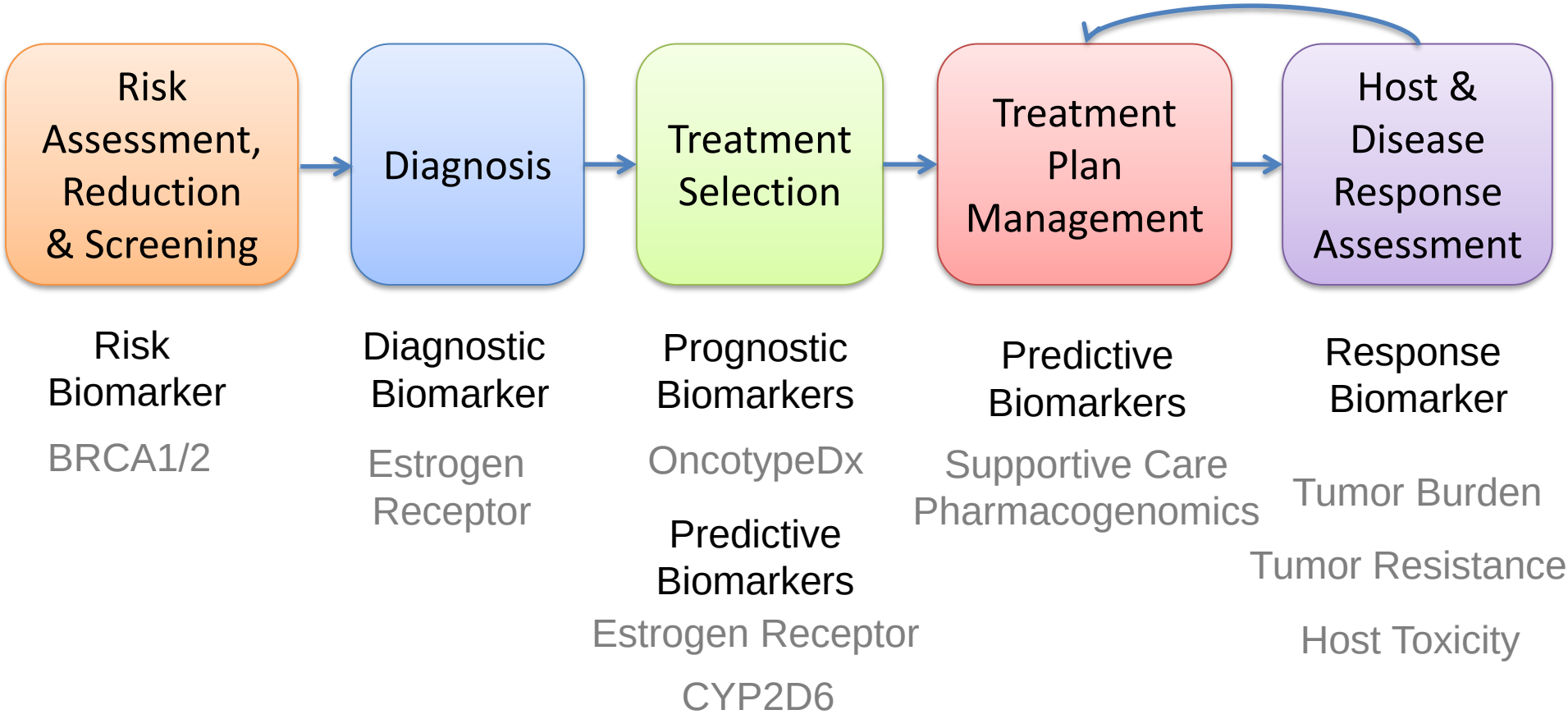
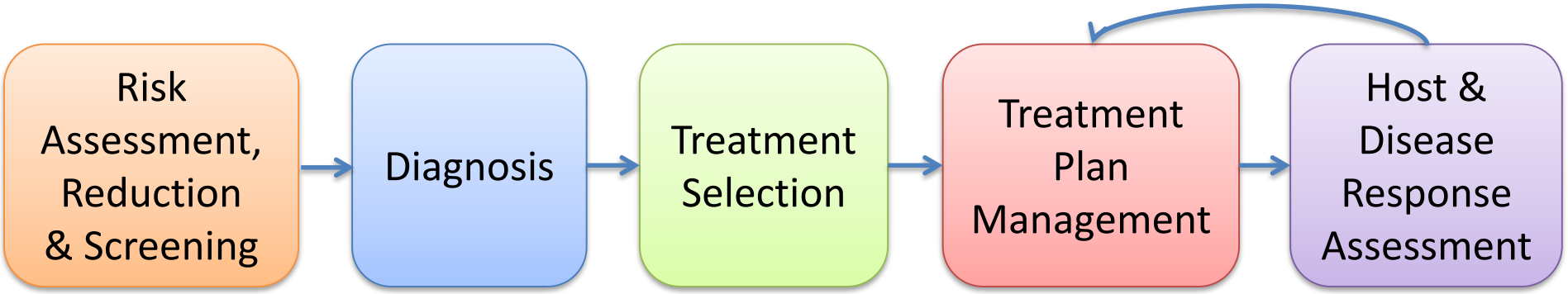
Cancer Care Continuum



Biomarkers in the Cancer Care Continuum



Decision Support
Cancer Care Continuum



Predictive Biomarkers

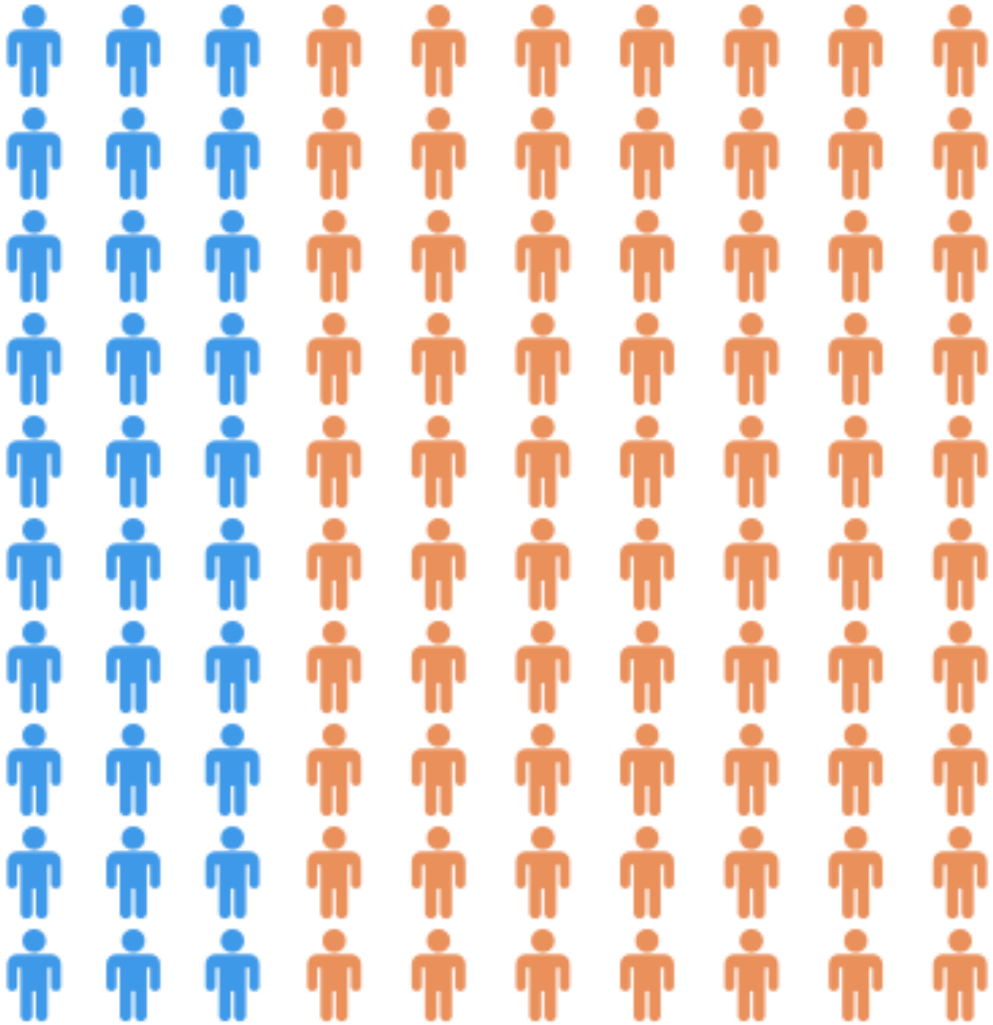
Types of Decision Support:
Which tests to order?
How to interpret and report results?
How to apply results to patient care?

Mode of Decision Support:
When
How
To Whom

Unselected Population

Treat Unselected

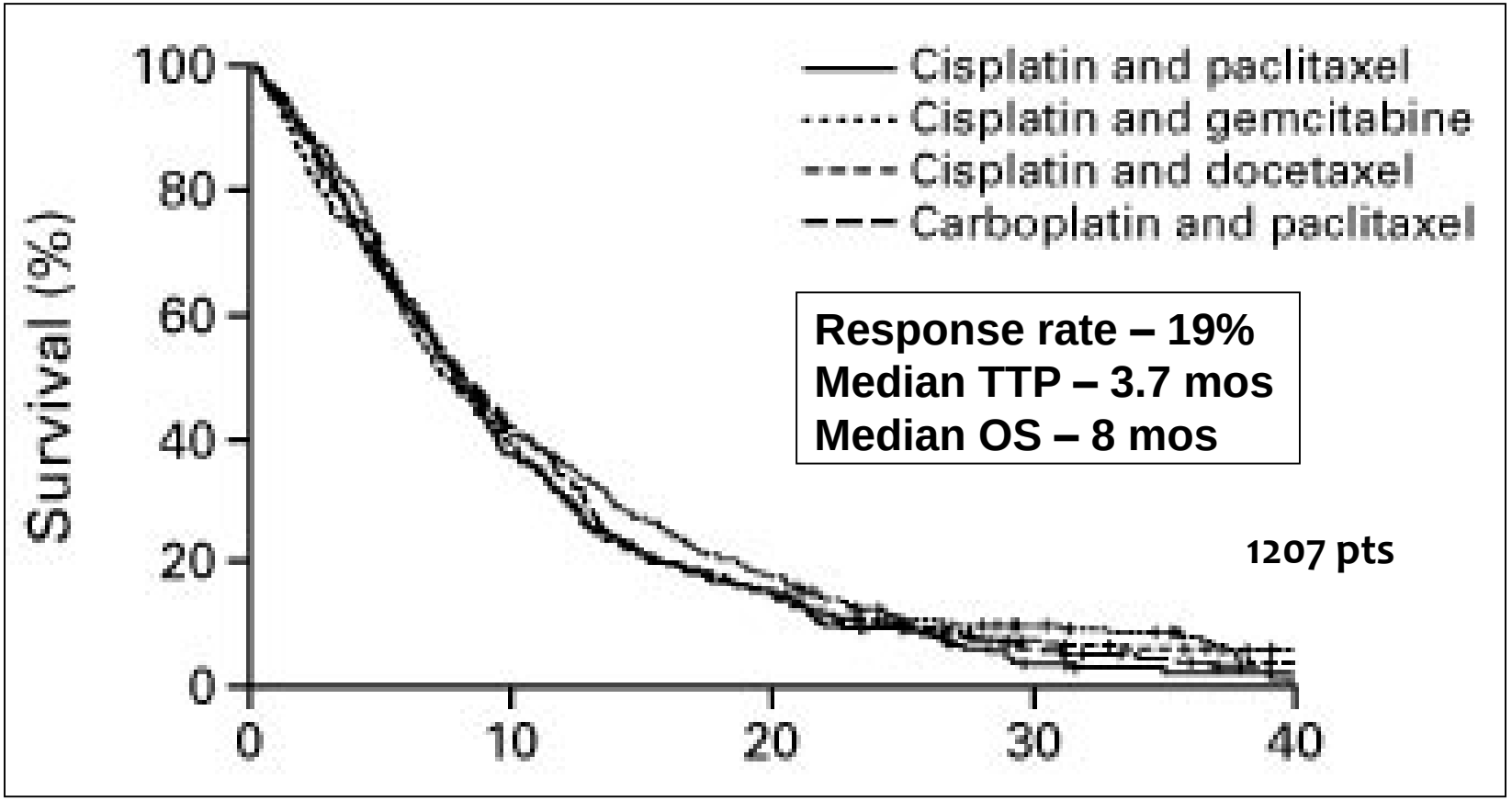
Response



No Response

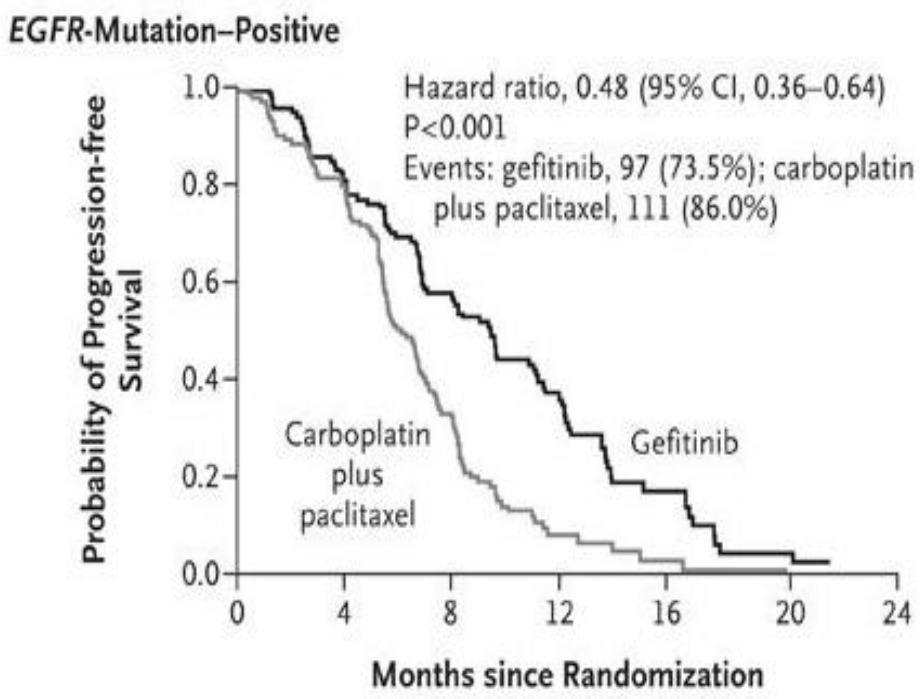
2002

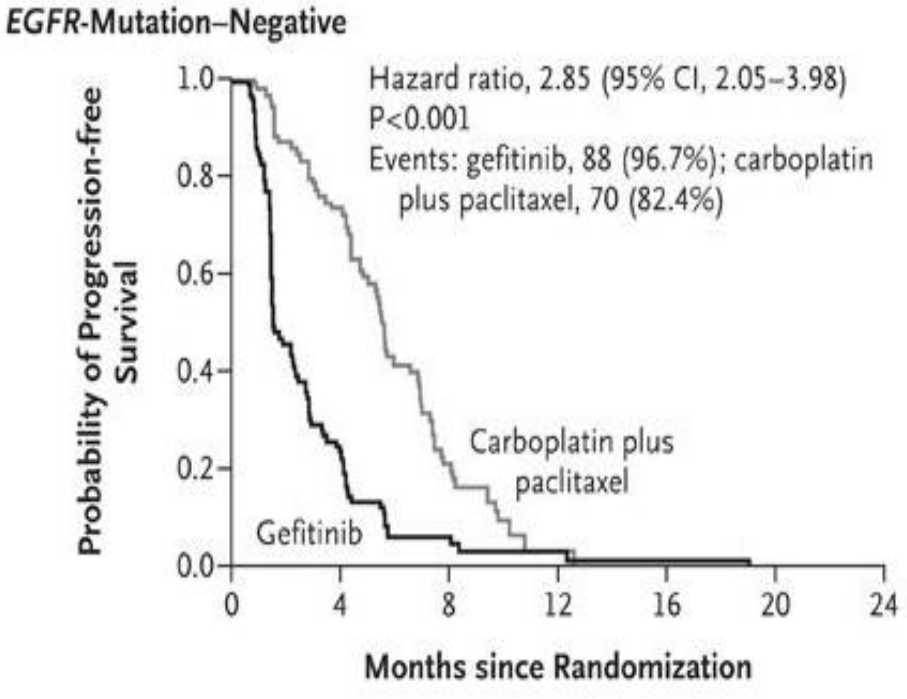
Comparison of 4 Chemotherapy Regimens in Advanced Lung Cancer



Schiller et al, *NEJM* '02

2009
EGFR mutated lung cancer



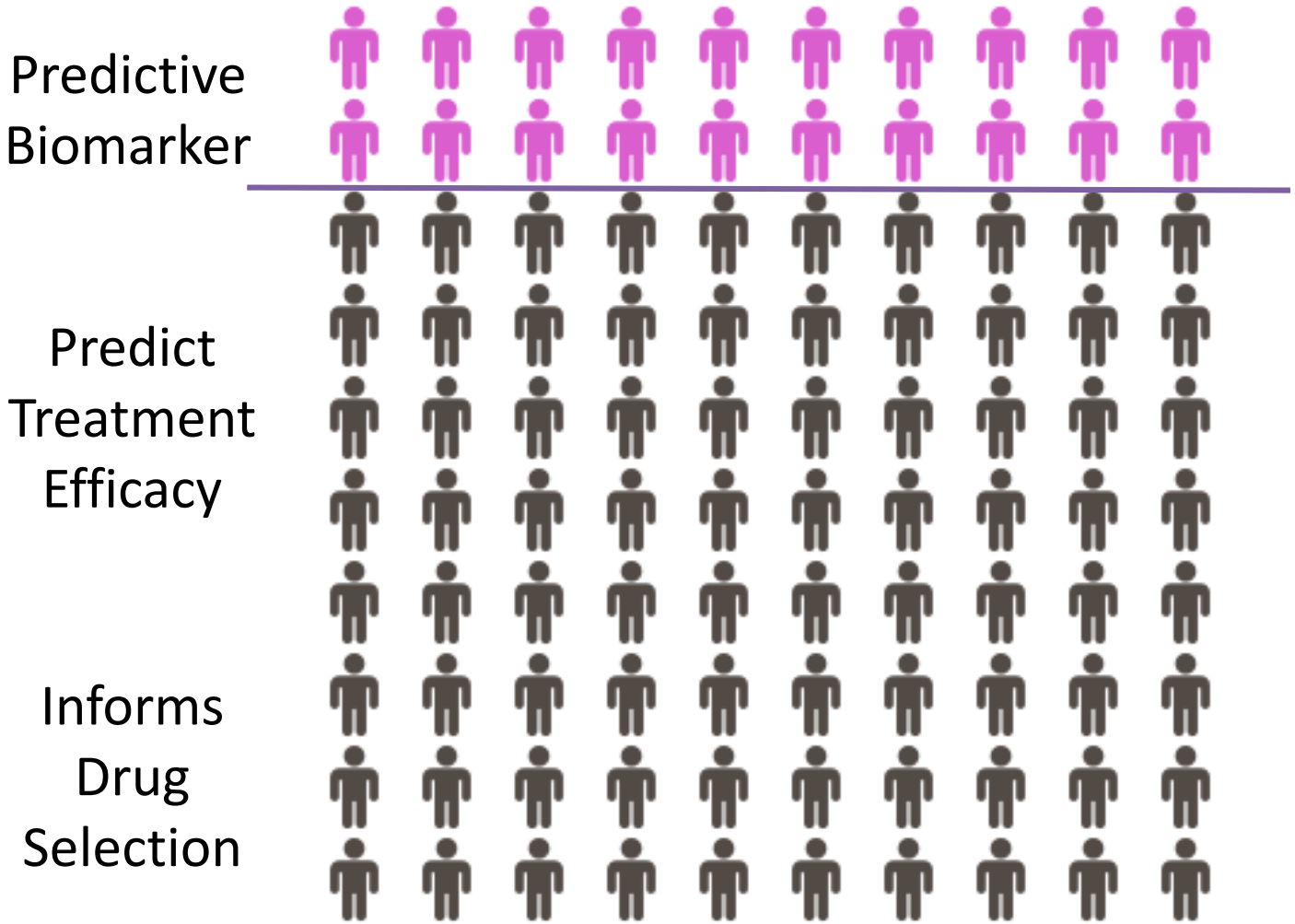


Initial phase III first line EGFR TKI trial: "IPASS"
EGFR TKI vs. Carboplatin - Paclitaxel
in Never- or Light Ex-Smokers

Ref: Mok et al NEJM 2009;
updated data Fukuouka et al JCO 2011

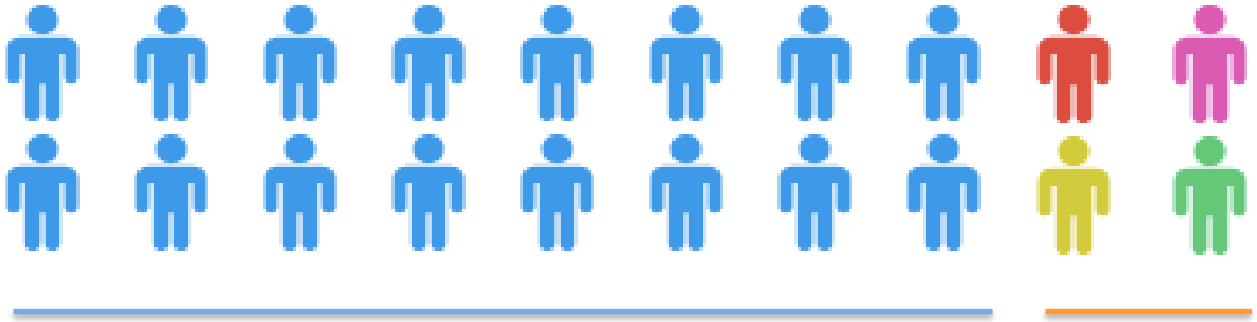
Unselected Population

Selected Population



Treat Selected

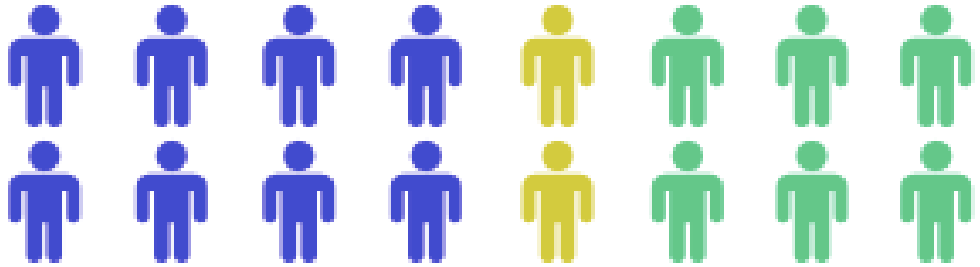
Targeted Therapy



Primary Sensitivity

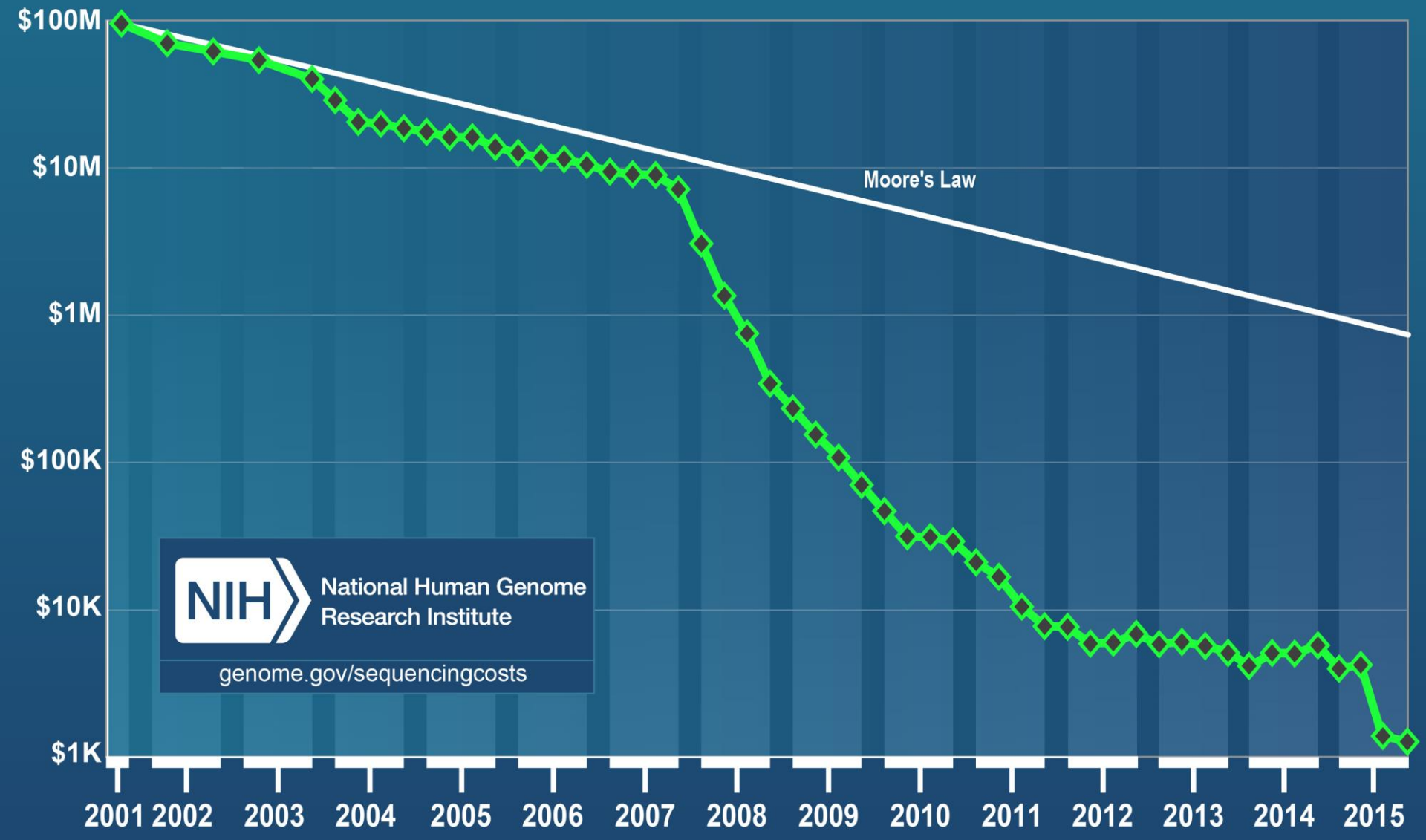
Primary Resistance

Disease Progress



Acquired Resistance

Cost per Genome



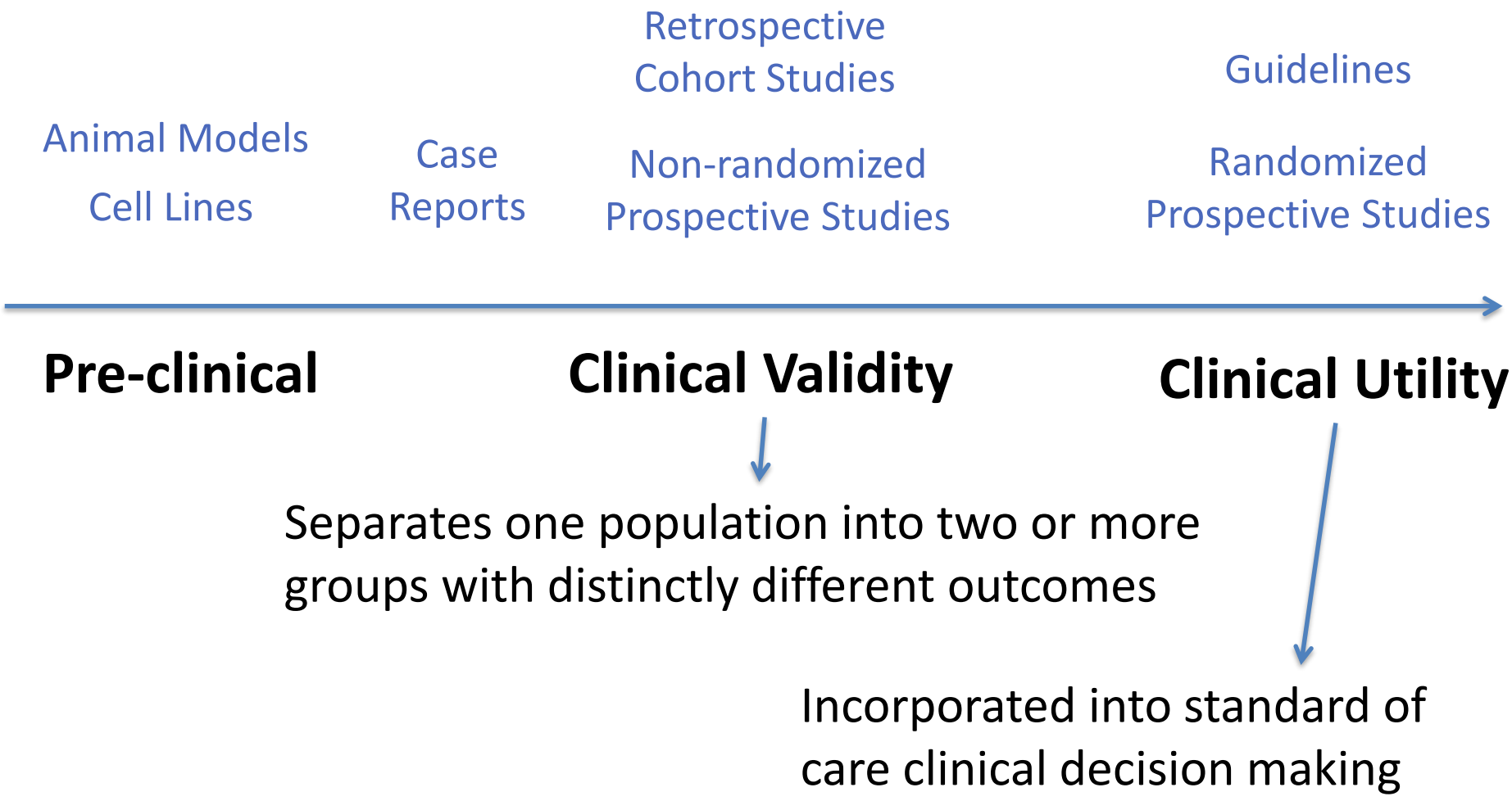
http://www.genome.gov/sequencingcosts/

Riding the Tsunami of Genomic Data

Evolution of testing strategies

Single mutation -> Hot spot panels -> NGS

Levels of Evidence

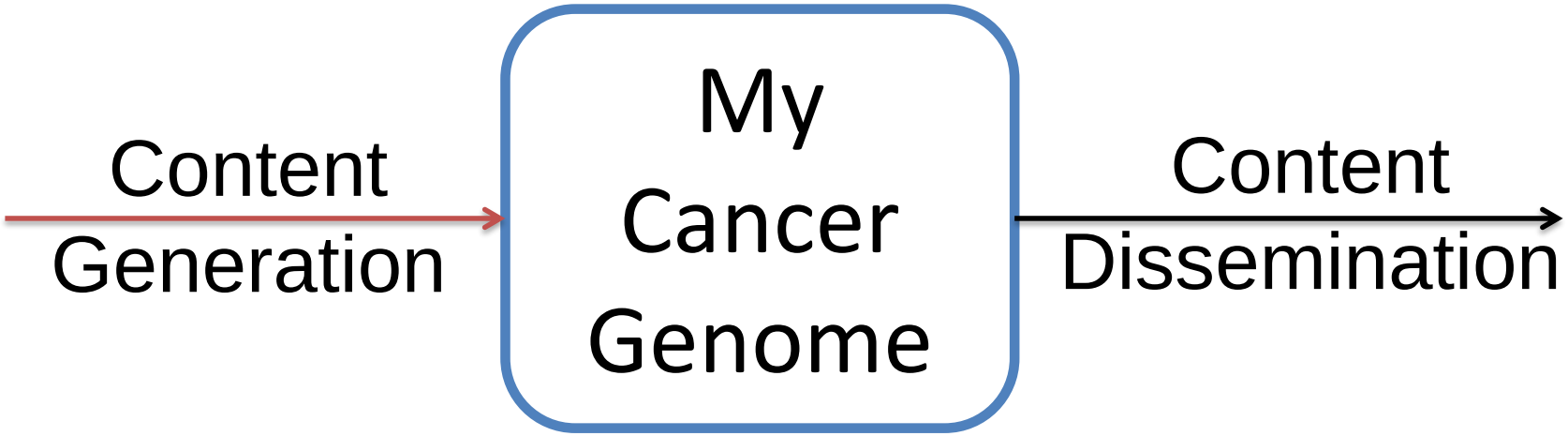


2016
Non-small cell lung cancer

Molecular alteration	Drugs	Level of evidence
EGFR mutation	erlotinib, gefitinib, afatinib	FDA approved
ALK rearrangements	crizotinib, ceritinib	FDA approved
EGFR T790M mutation	osimertrinib	FDA approved
PD-L1 expression	pembrolizumab	FDA approved
BRAF mutation	Trametinib, dabrafenib	FDA approved
ROS1 rearrangements	crizotinib	FDA approved
MET amplifications	crizotinib	NCCN
HER2 mutations	trastuzumab, afatinib	NCCN
KRAS mutations	Resistance to TKI's	NCCN

Mission of My Cancer Genome

To curate and disseminate knowledge regarding the clinical significance of genomic alterations in cancer


Content
Generation
My
Cancer
Genome
Content
Dissemination

My Cancer Genome

Genetically Informed Cancer Medicine

Search My Cancer Genome

Go

Find a Cancer Mutation

Disease (required): Select Disease

Gene (optional):

Variant (optional):

GO

Manually Curated Content

21 Cancers

ALL
ALCL
AML
CML
MDS
GIST
IMT
Breast
Glioma
Gastric
Lung
Colorectal
Basal Cell Carcinoma
Bladder
Medulloblastoma
Melanoma
Neuroblastoma
Ovarian
Rhabdomyosarcoma
Thymic
Thyroid

20 Pathways
823 Genes
21 Cancers
429 Variants
552 Drugs

More...

My Cancer Genome™

Genetically Informed Cancer Medicine

Find a Cancer Mutation

Disease (required): Select Disease

Gene (optional): Select Disease First

Variant (optional): Select Disease First

GO

Find Clinical Trials

Lists trials by Disease or Gene for all national and international trials registered within PDQ and clinicaltrials.gov.

My Cancer Genome™

Genetically Informed Cancer Medicine

Find a Cancer Mutation

Disease (required):

Gene (optional):

Variant (optional):

- ✓ Select Disease
- Acute Lymphoblastic Leukemia
- Acute Myeloid Leukemia
- Anaplastic Large Cell Lymphoma
- Basal Cell Carcinoma
- Bladder Cancer
- Breast Cancer
- Chronic Myeloid Leukemia
- Colorectal Cancer
- Gastric Cancer
- GIST
- Glioma
- Inflammatory Myofibroblastic Tumor
- Lung Cancer
- Medulloblastoma
- Melanoma
- Myelodysplastic Syndromes
- Neuroblastoma
- Ovarian Cancer
- Rhabdomyosarcoma
- Thymic Carcinoma
- Thyroid Cancer

Find Clinical Tria

Lists trials by Dis

trials registered

My Cancer Genome™

Genetically Informed Cancer Medicine

Find a Cancer Mutation

Disease (required): Lung Cancer

Gene (optional): ✓ Select Gene
AKT1
ALK
BRAF
DDR2
EGFR
FGFR1
HER2
KRAS
MEK1
MET
NRAS
NTRK1
PIK3CA
PTEN
RET
ROS1

Variant (optional):

Find Clinical Tria

Lists trials by Dis Gene for all national and international trials registered within PDQ and clinicaltrials.gov.

My Cancer Genome™

Genetically Informed Cancer Medicine

Find a Cancer Mutation

Disease (required): Lung Cancer

Gene (optional): EGFR

Variant (optional): ✓ Select Variant

- EGFR Status Unknown
- EGFR No Mutation Detected
- EGFR c.2156G>C (G719A)
- EGFR c.2155G>T (G719C)
- EGFR c.2155G>A (G719S)
- EGFR Exon 19 Deletion
- EGFR Exon 19 Insertion
- EGFR Exon 20 Insertion
- EGFR c.2290_2291ins (A763_Y764insFQEA)
- EGFR c.2369C>T (T790M)
- EGFR c.2573T>G (L858R)
- EGFR c.2582T>A (L861Q)

Find Clinical Tria

Lists trials by Disease or Gene for all national and international trials registered within PDQ and clinicaltrials.gov.

MY CANCER GENOME™

GENETICALLY INFORMED CANCER MEDICINE

Find a Cancer Mutation

Disease (required): Lung Cancer

Gene (optional): EGFR

Variant (optional): EGFR c.2369C>T (T790M)

GO

Find Clinical Trials

Lists trials by Disease or Gene for all national and international trials registered within PDQ and clinicaltrials.gov.

What is EGFR? | EGFR in Lung Cancer | EGFR c.2369C>T (T790M) | Clinical Trials

EGFR c.2369C>T (T790M) Mutation in Non-Small Cell Lung Cancer

Properties	
Location of mutation	Kinase domain (exon 20)
Frequ…	…USA …Paez et al. 2004; Pao et al. 2004)
R…	…*GFR* mutant tumors (Inukai et al. 2006) …nt tumors with acquired resistance to …obayashi et al. 2005; Pao et al. 2005)
I…	
R…	…sensitivity
R…	…sensitivity
R… EG…	…sensitivity
Response to anti-EGFR antibodies	Currently no role for *EGFR*

Location of Alteration in Gene

Levels of Evidence

- FDA Approvals
- Guidelines
- Published clinical trial results
- Retrospective cohort analysis
- Case Reports
- Clinical trial eligibility criteria
- Pre-clinical studies

Frequency of Alteration in Disease

Response to Drug Sensitivity/Resistance

What	Reference
EG Car	Miller et al. 2012
Prope	
Locat	
Frequ	Katakami et al. 2013
Frequ mutat	Janjigian et al. 2014
Implic	
Respo (erloti	Sequist et al. 2014 [presentation]; Soria et al. 2013
Respo (afatir	
Respo EGFR	Jänne et al. 2014; Ranson et al. 2013
Respo	Kim et al. 2014 [presentation]

Cancer Discov. 2014 Sep;4(9):1036-45. doi: 10.1158/2159-8290.CD-14-0326. Epub 2014 Jul 29.

Dual inhibition of EGFR with afatinib and cetuximab in kinase inhibitor-resistant EGFR-mutant lung cancer with and without T790M mutations.

Janjigian YY[1], Smit EF[2], Groen HJ[3], Horn L[4], Gettinger S[5], Camidge DR[6], Riely GJ[7], Wang B[8], Fu Y[8], Chand VK[8], Miller VA[7], Pao W[4].

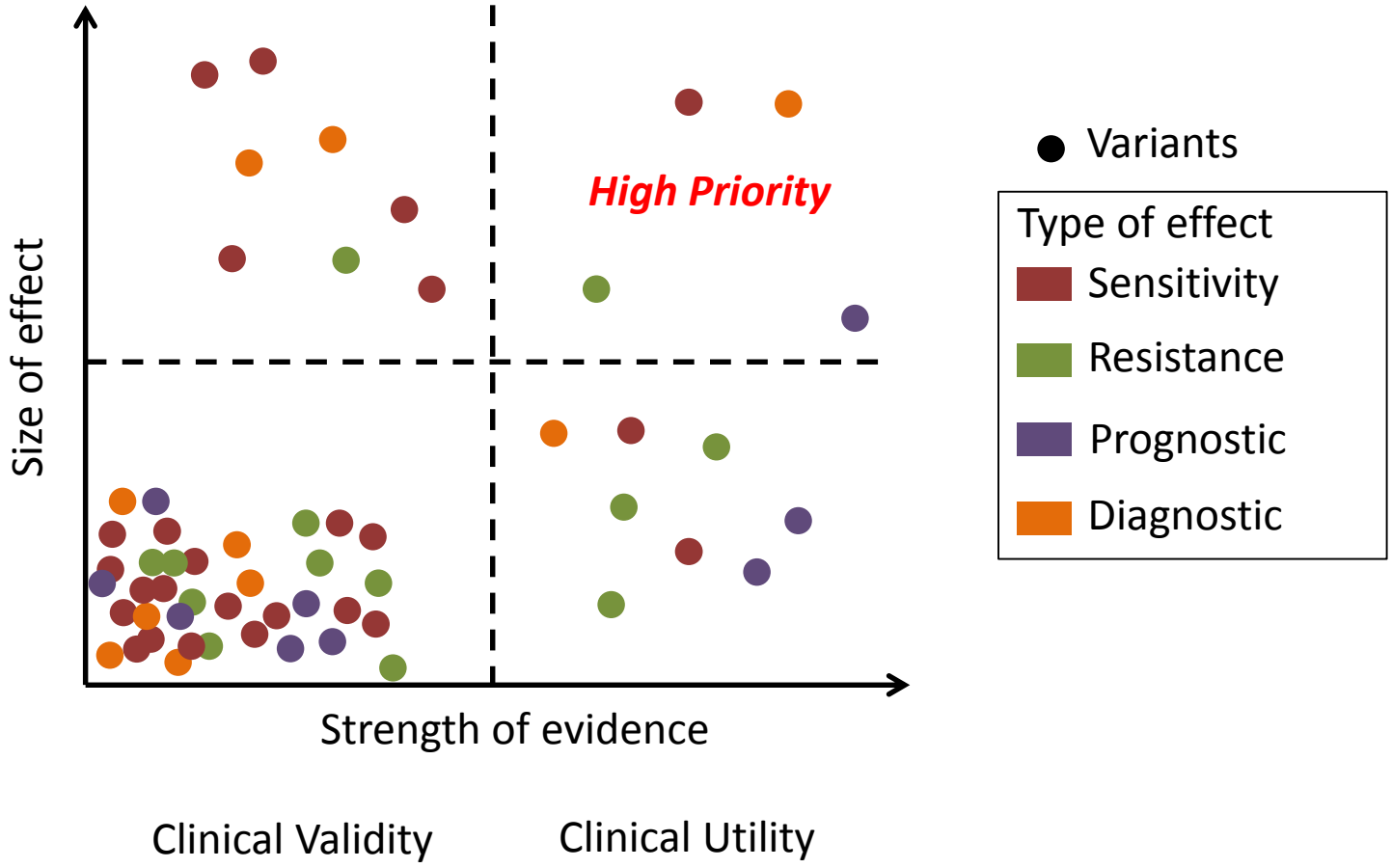
Author information

Abstract

EGFR-mutant lung cancers responsive to reversible EGFR inhibitors (gefitinib/erlotinib) develop acquired resistance, mediated by second-site EGFR T790M mutation in >50% of cases. Preclinically, afatinib (irreversible ErbB family blocker) plus cetuximab (anti-EGFR monoclonal antibody) overcomes T790M-mediated resistance. This phase Ib study combining afatinib and cetuximab enrolled heavily pretreated patients with advanced EGFR-mutant lung cancer and acquired resistance to erlotinib/gefitinib. Patients provided post-acquired-resistance tumor samples for profiling EGFR mutations. Among 126 patients, objective response rate (overall 29%) was comparable in T790M-positive and T790M-negative tumors (32% vs. 25%; P = 0.341). Median progression-free survival was 4.7 months (95% confidence interval, 4.3-6.4), and the median duration of confirmed objective response was 5.7 months (range, 1.8-24.4). Therapy-related grade 3/4 adverse events occurred in 44%/2% of patients. Afatinib-cetuximab demonstrated robust clinical activity and a manageable safety profile in EGFR-mutant lung cancers with acquired resistance to gefitinib or erlotinib, both with and without T790M mutations, warranting further investigation.

SIGNIFICANCE: This article reports the results of a trial combining afatinib and cetuximab in patients with acquired resistance and details the first clinical proof-of-concept for the preclinical hypothesis that a significant proportion of tumors in patients with acquired resistance to gefitinib/erlotinib remain dependent on EGFR signaling for survival.

Biomarker Classification & Prioritization

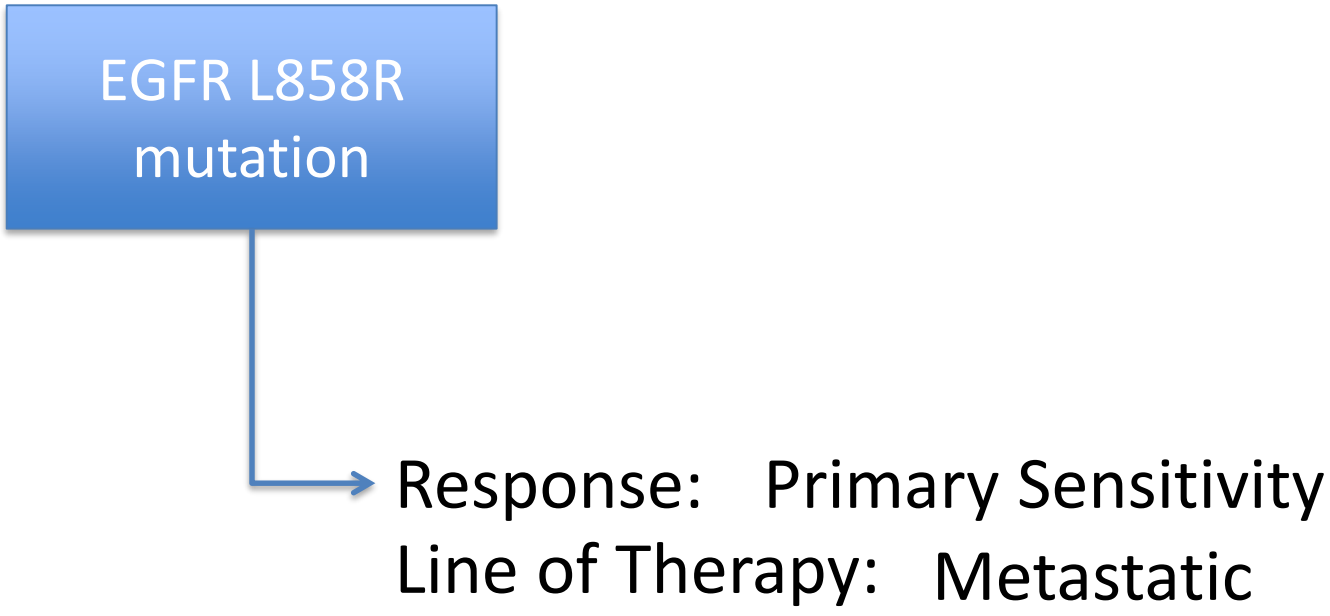


JCO, Levy 2013

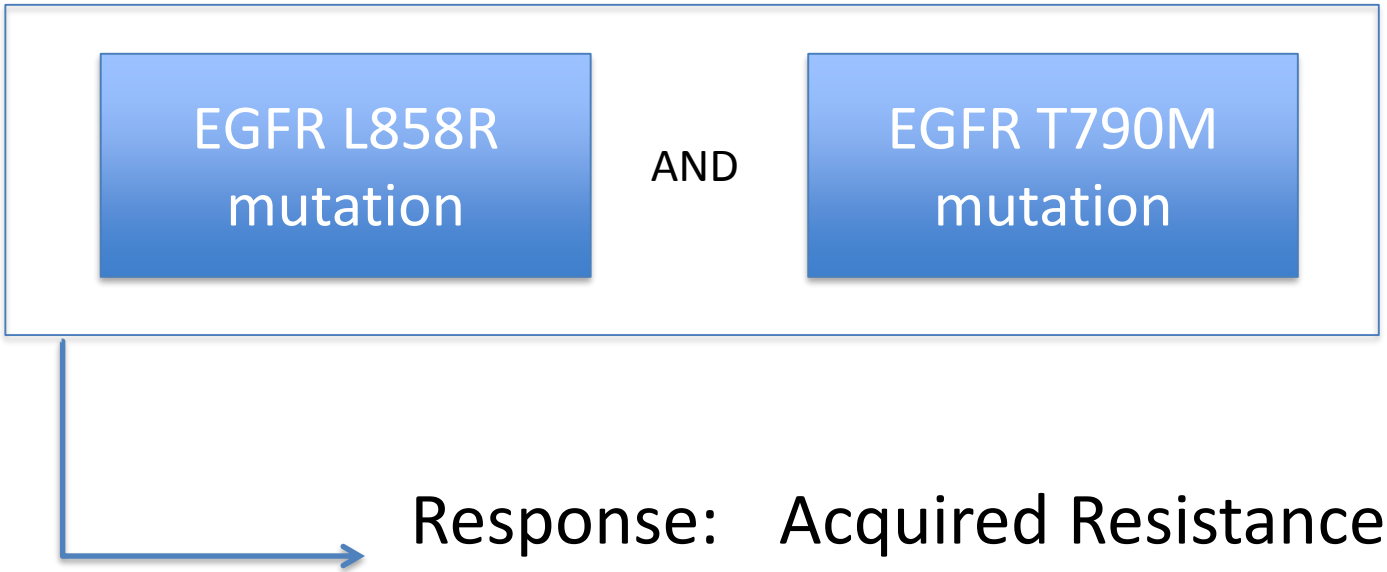
Biomarker Representation

- **Types of Biomarkers**
  - Gene Variant (point mutations, insertions, deletions)
  - Exon
  - Fusions/Rearrangements
  - Gene Amplification
  - Protein Expression
- **Logical Combinations of Alterations**
  - AND/OR/NOT

Therapy Assertion
Lung Cancer & Erlotinib
(single alteration)

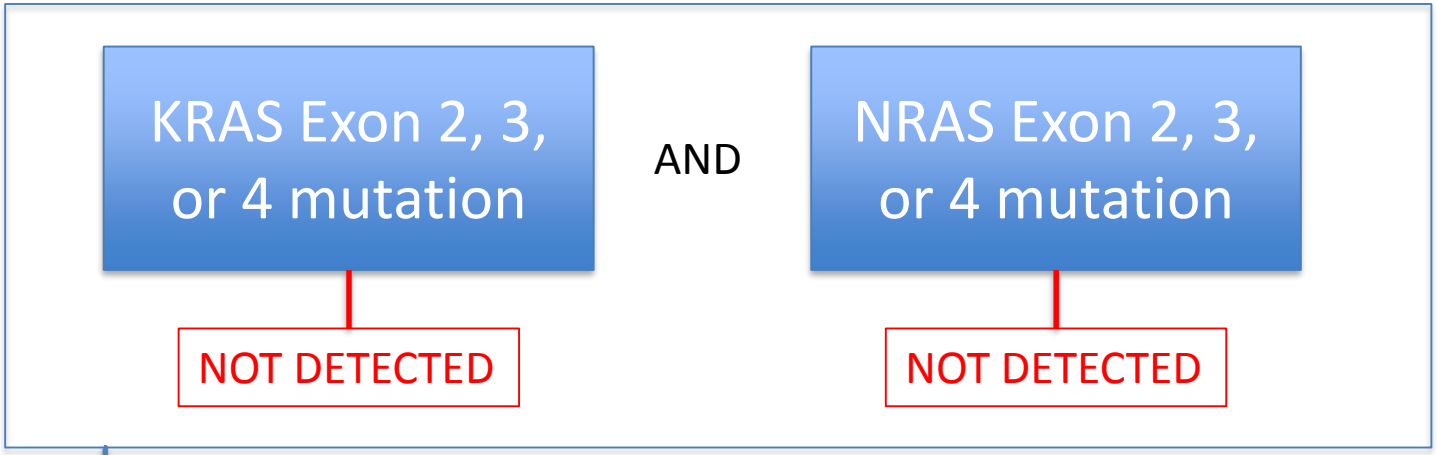


Therapy Assertions
Lung Cancer & Erlotinib
(co-occuring alterations)



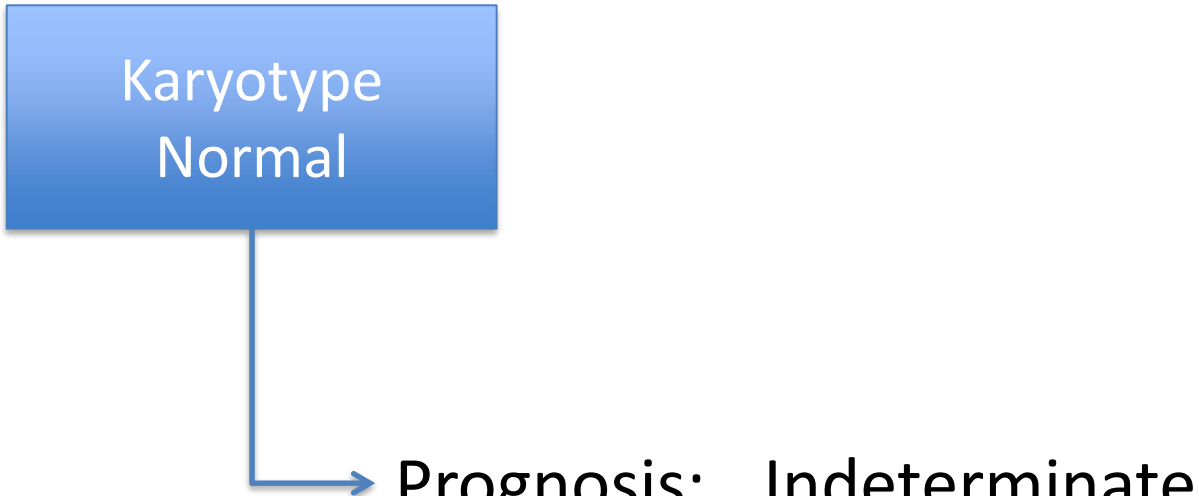
Therapy Assertion
Colon Cancer & Cetuximab

(Alteration NOT detected in Variant Group)

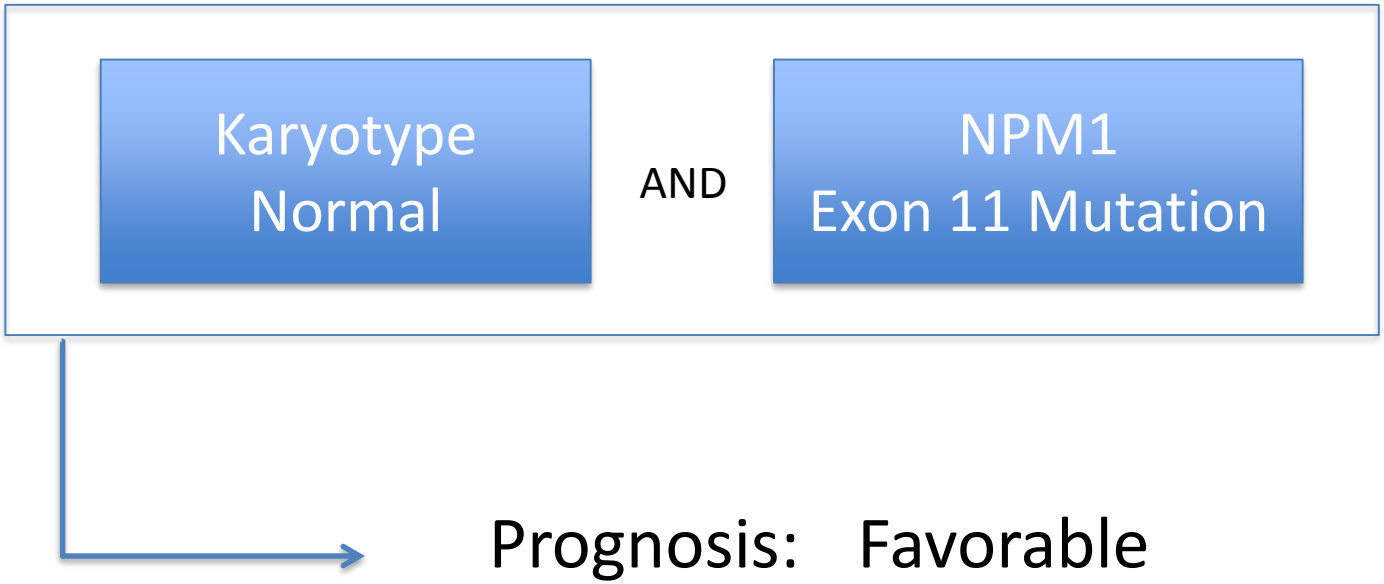


Response: Primary Sensitivity
Line of Therapy: Metastatic
Source: FDA (KRAS Exon 2)
Source: NCCN (KRAS Exon 2, 3, 4)
Source: ASCO (KRAS Exon 2)

Prognostic Assertion
Acute Myeloid Leukemia
(single alteration)

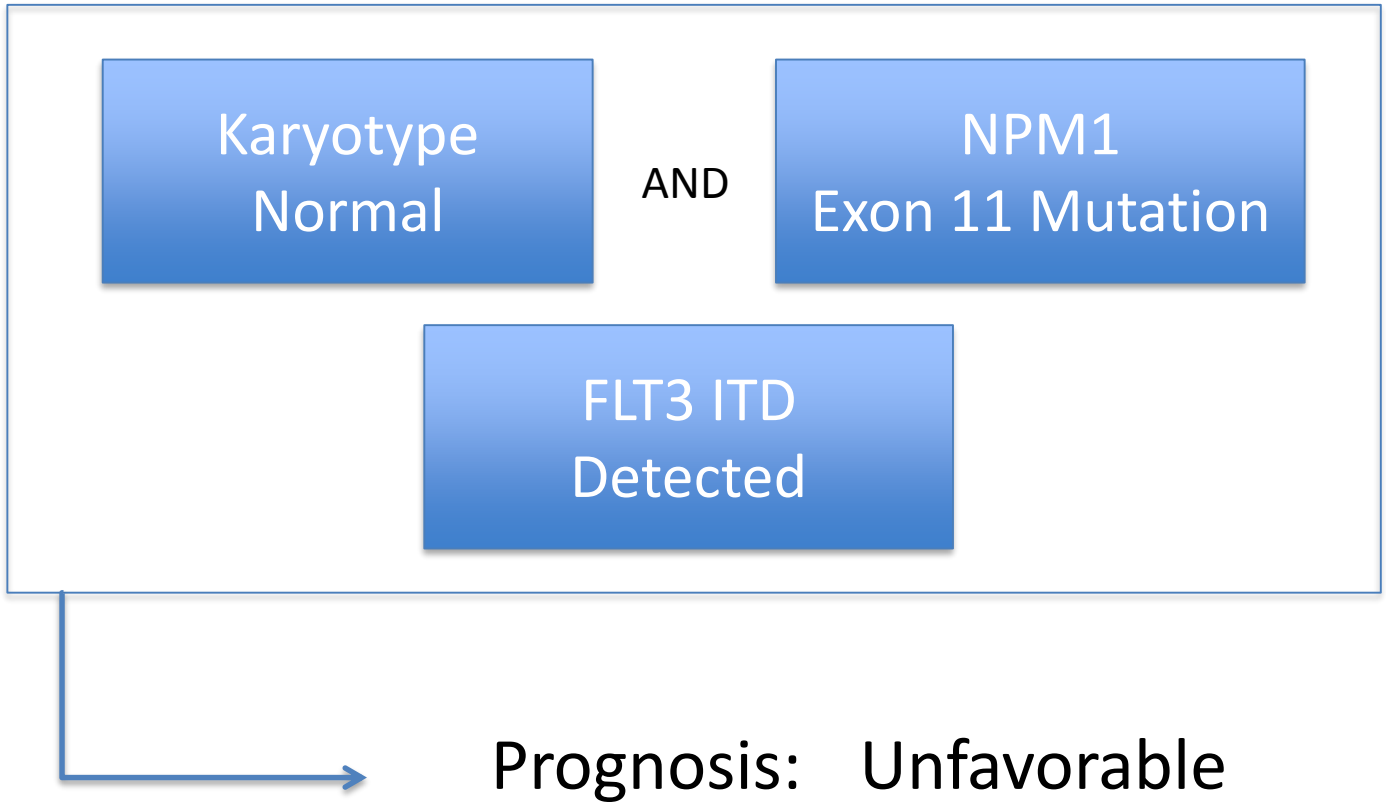


Prognostic Assertion
Acute Myeloid Leukemia
(co-occuring alterations)



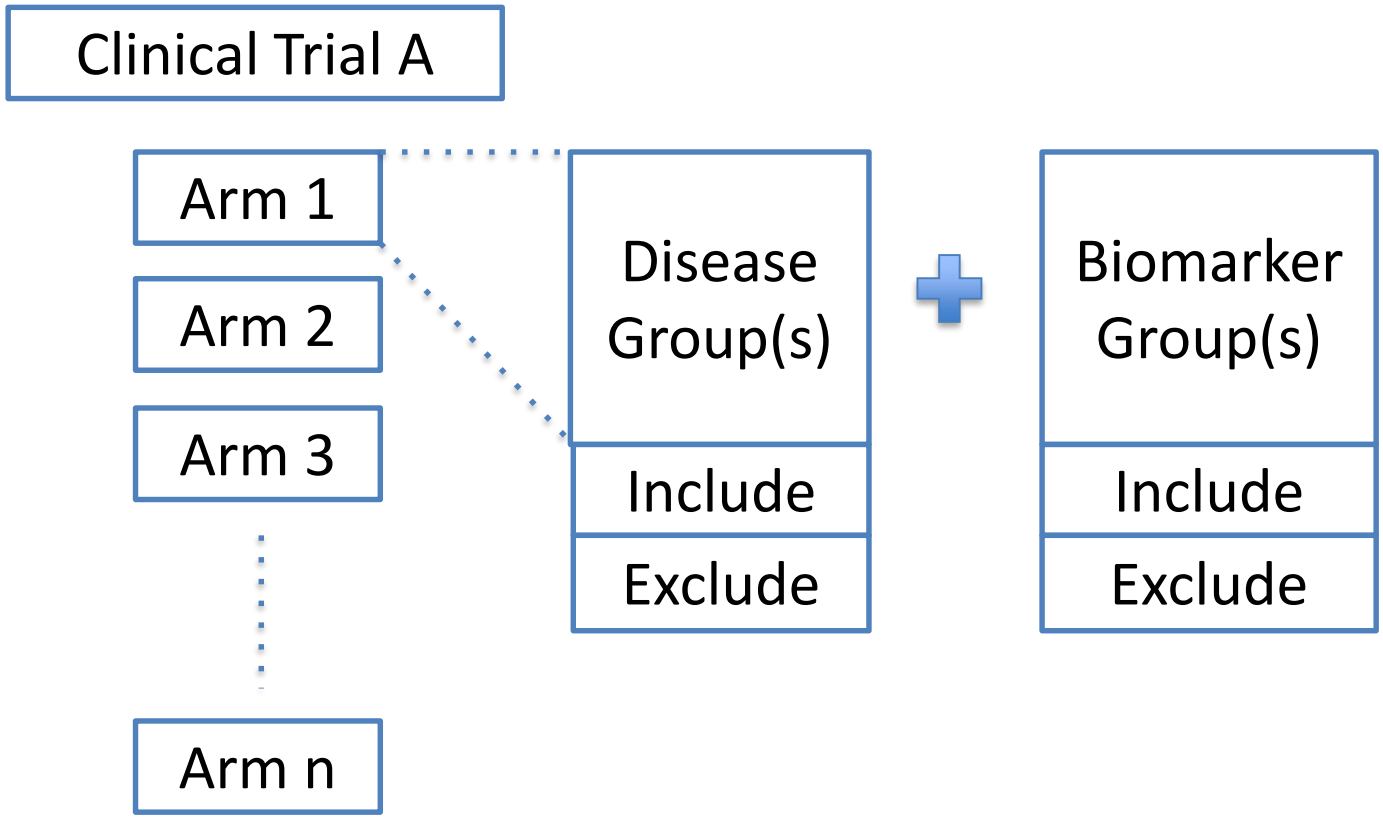
Prognosis: Favorable
Source: NCCN

Prognostic Assertion
Acute Myeloid Leukemia
(co-occuring alterations)

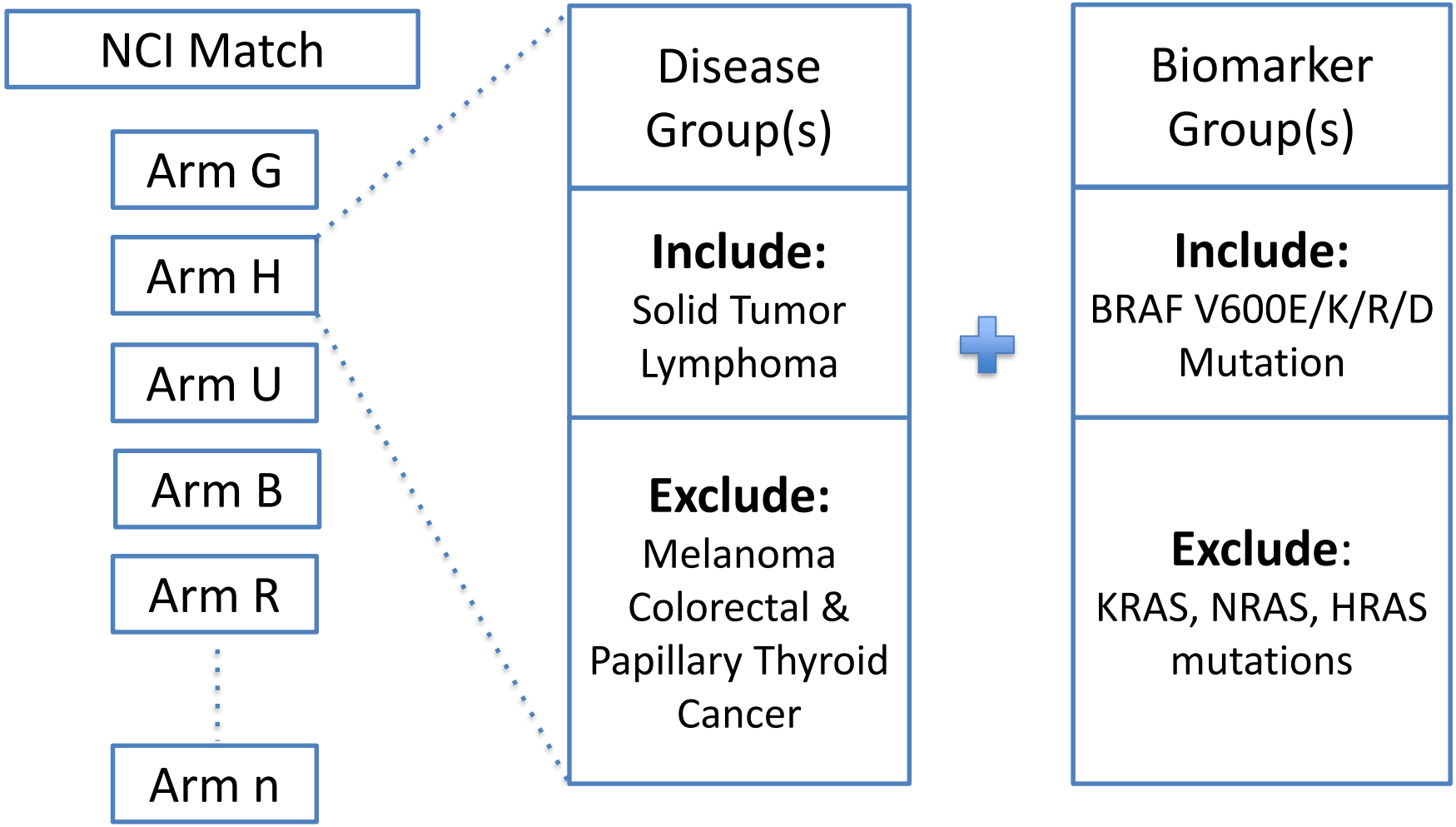


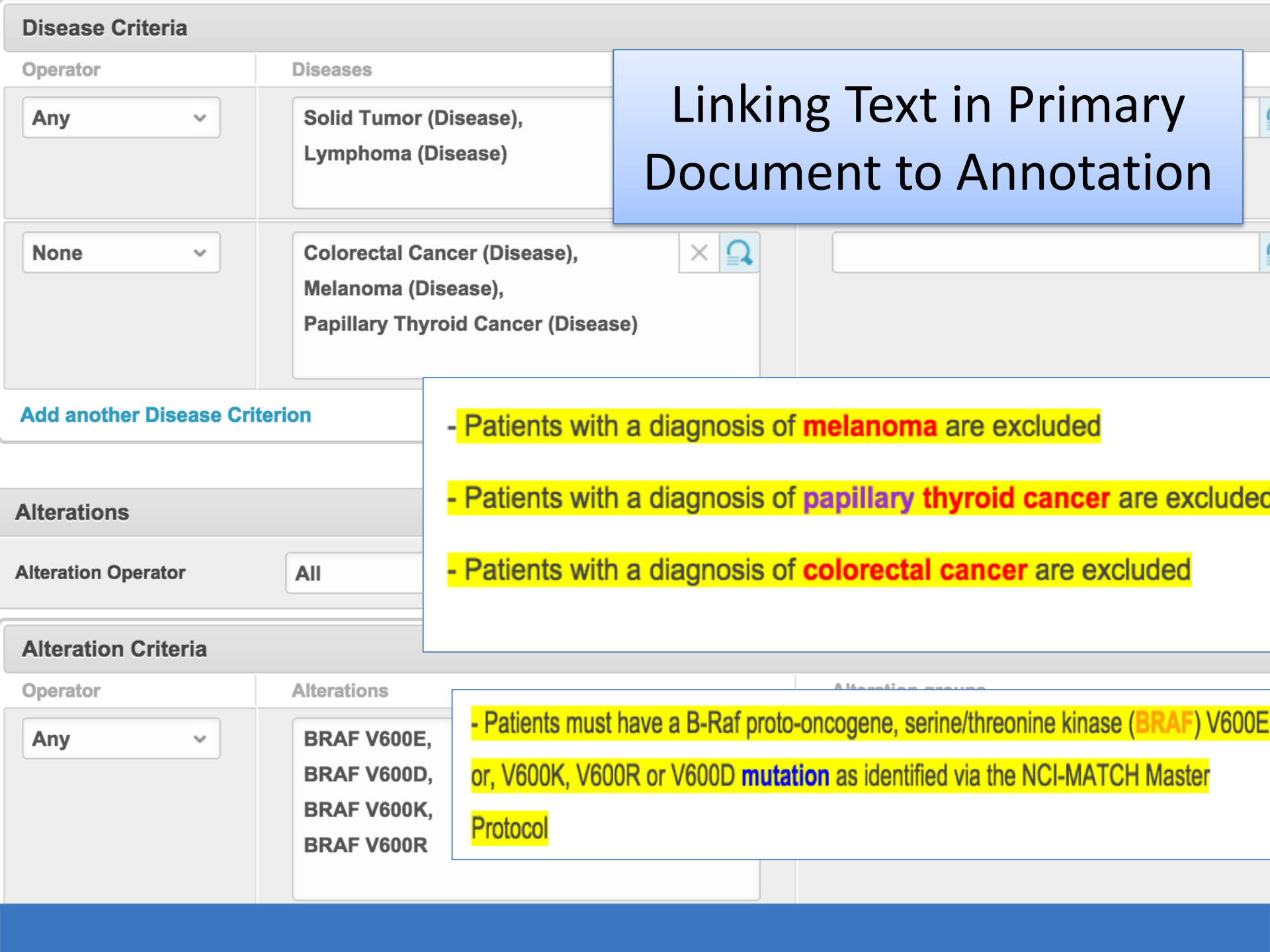
Prognosis: Unfavorable
Source: NCCN

Clinical Trial Annotation

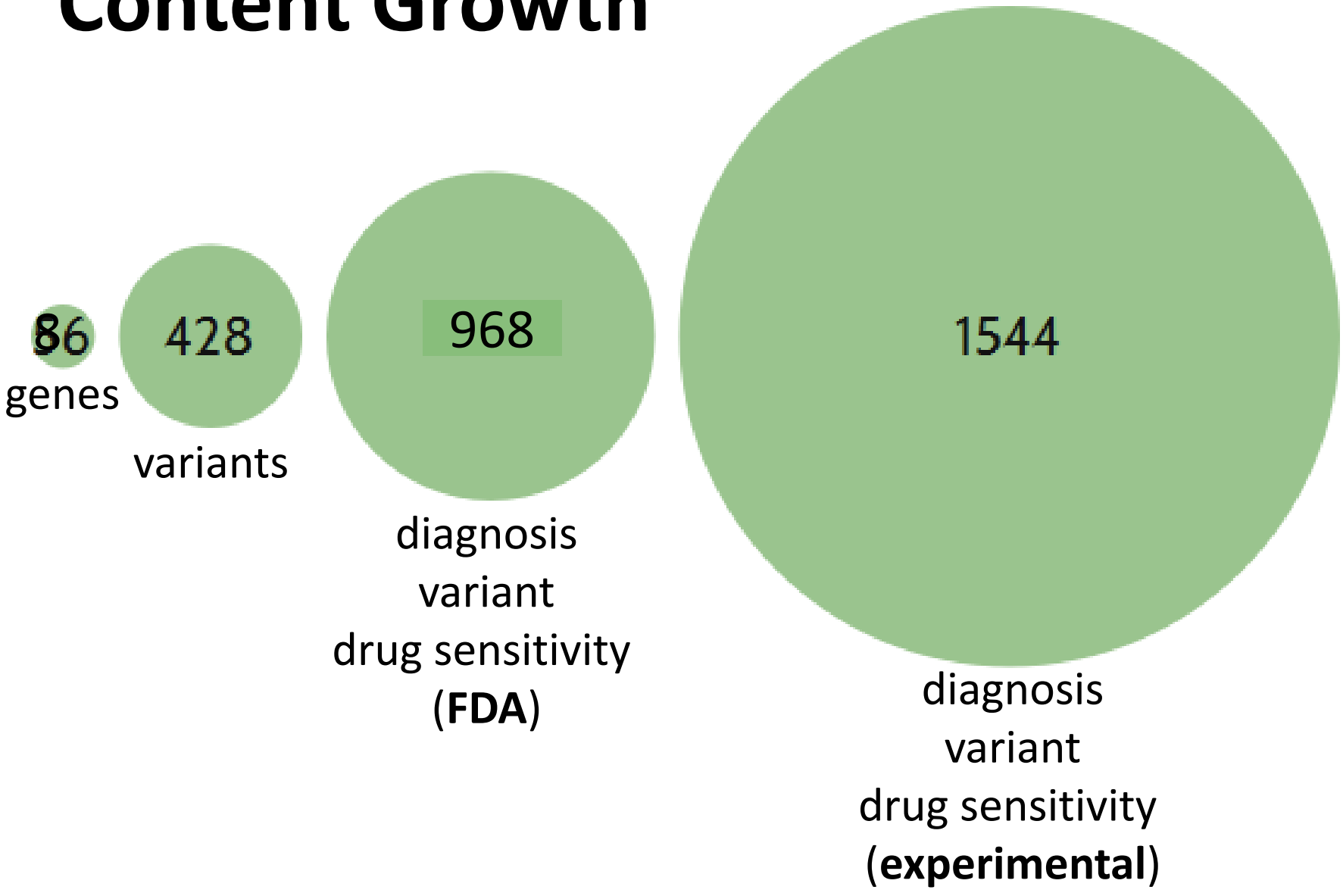


Example: NCI Match

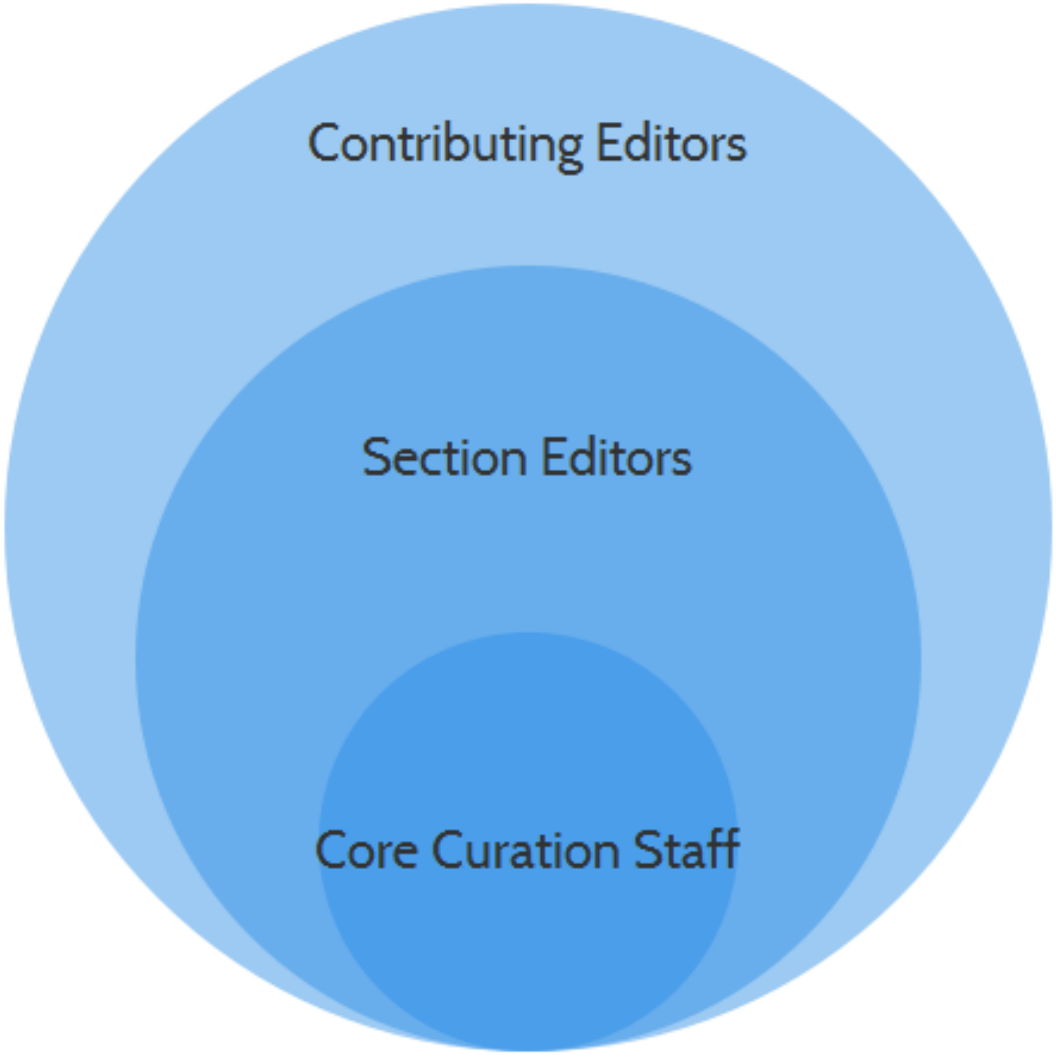



Disease Criteria
Operator
Diseases
Any
Solid Tumor (Disease),
Lymphoma (Disease)
None
Colorectal Cancer (Disease),
Melanoma (Disease),
Papillary Thyroid Cancer (Disease)
Add another Disease Criterion
Linking Text in Primary Document to Annotation
- Patients with a diagnosis of melanoma are excluded
- Patients with a diagnosis of papillary thyroid cancer are excluded
- Patients with a diagnosis of colorectal cancer are excluded
Alterations
Alteration Operator
All
Alteration Criteria
Operator
Alterations
Any
BRAF V600E,
BRAF V600D,
BRAF V600K,
BRAF V600R
- Patients must have a B-Raf proto-oncogene, serine/threonine kinase (BRAF) V600E
or, V600K, V600R or V600D mutation as identified via the NCI-MATCH Master
Protocol

Content Growth



Contributor Network



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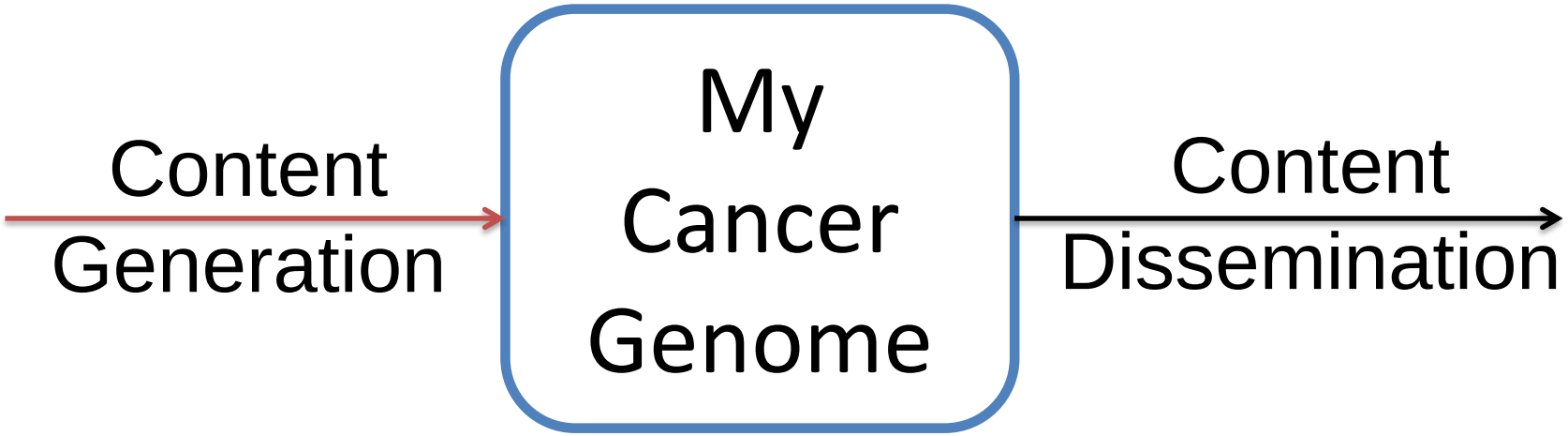

Content
Generation
My
Cancer
Genome
Content
Dissemination

Dissemination

Publically Available Resources

Website

>2.5M page views, 201 countries

Mobile App

>3634 Downloads, 22K sessions

My Cancer Genome

Clinically Integrated Solutions

Vanderbilt EHR

>5800 patients

Laboratory Reporting Tool

>3200 specimens

New Method for Reporting Mutation Results in the EHR

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							

Order Status (letter)

- O = Order Received
- R = Outside Specimen Requested
- A = Outside Specimen Arrived
- v = Specimen Accessioned

Result Status (colored box)

- Yellow = Gene Mutation Detected
- Grey = Gene Mutation Not Detected
- Red = No Result – Insufficient Specimen

Levy, ASCO 2011

Levy, Genome Research 2012

New Method for Reporting Mutation Results in the EHR

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
BRAF c.1799T>A (V600E)	Detected
BRAF c.1799_1800TG>AA (V600E)	Not Detected
BRAF c.1798G>A (V600M)	Not Detected
BRAF c.1799T>G (V600G)	Not Detected
BRAF c.1799_1800TG>AT (V600D)	Not Detected

Levy, ASCO 2011

Levy, Genome Research 2012

New Method for Reporting Mutation Results in the EHR

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							

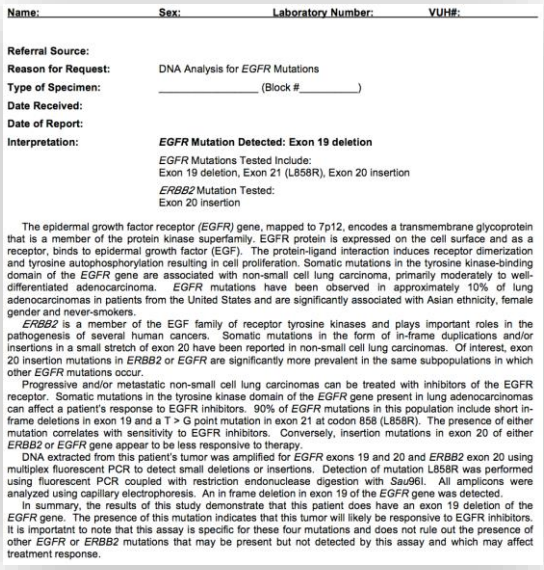
- Primary Sensitivity
- Primary Resistance
- Secondary Resistance

BRAF c.1798_1799GT>AG (V600R)	Not Detected
BRAF c.1798_1799GT>AA (V600K)	Not Detected
BRAF c.1799T>A (V600E)	Detected
BRAF c.1799_1800TG>AA (V600E)	Not Detected
BRAF c.1798G>A (V600M)	Not Detected
BRAF c.1799T>G (V600G)	Not Detected
BRAF c.1799_1800TG>AT (V600D)	Not Detected

Levy, ASCO 2011
Levy, Genome Research 2012

Scale Reporting

1 Variant
1 Gene



Name: **Sex:** **Laboratory Number:** **VUH#:**

Referral Source:
Reason for Request: DNA Analysis for *EGFR* Mutations
Type of Specimen: _____ (Block #_____)
Date Received:
Date of Report:
Interpretation: ***EGFR* Mutation Detected: Exon 19 deletion**

EGFR Mutations Tested Include:
Exon 19 deletion, Exon 21 (L858R), Exon 20 insertion

ERBB2 Mutation Tested:
Exon 20 insertion

The epidermal growth factor receptor *(EGFR)* gene, mapped to 7p12, encodes a transmembrane glycoprotein that is a member of the protein kinase superfamily. EGFR protein is expressed on the cell surface and as a receptor, binds to epidermal growth factor (EGF). The protein-ligand interaction induces receptor dimerization and tyrosine autophosphorylation resulting in cell proliferation. Somatic mutations in the tyrosine kinase-binding domain of the *EGFR* gene are associated with non-small cell lung carcinoma, primarily moderately to well-differentiated adenocarcinoma. *EGFR* mutations have been observed in approximately 10% of lung adenocarcinomas in patients from the United States and are significantly associated with Asian ethnicity, female gender and never-smokers.

ERBB2 is a member of the EGF family of receptor tyrosine kinases and plays important roles in the pathogenesis of several human cancers. Somatic mutations in the form of in-frame duplications and/or insertions in a small stretch of exon 20 have been reported in non-small cell lung carcinomas. Of interest, exon 20 insertion mutations in *ERBB2* or *EGFR* are significantly more prevalent in the same subpopulations in which other *EGFR* mutations occur.

Progressive and/or metastatic non-small cell lung carcinomas can be treated with inhibitors of the EGFR receptor. Somatic mutations in the tyrosine kinase domain of the *EGFR* gene present in lung adenocarcinomas can affect a patient's response to EGFR inhibitors. 90% of *EGFR* mutations in this population include short in-frame deletions in exon 19 and a T > G point mutation in exon 21 at codon 858 (L858R). The presence of either mutation correlates with sensitivity to EGFR inhibitors. Conversely, insertion mutations in exon 20 of either *ERBB2* or *EGFR* gene appear to be less responsive to therapy.

DNA extracted from this patient's tumor was amplified for *EGFR* exons 19 and 20 and *ERBB2* exon 20 using multiplex fluorescent PCR to detect small deletions or insertions. Detection of mutation L858R was performed using fluorescent PCR coupled with restriction endonuclease digestion with *Sau*96I. All amplicons were analyzed using capillary electrophoresis. An in frame deletion in exon 19 of the *EGFR* gene was detected.

In summary, the results of this study demonstrate that this patient does have an exon 19 deletion of the *EGFR* gene. The presence of this mutation indicates that this tumor will likely be responsive to EGFR inhibitors. It is importatnt to note that this assay is specific for these four mutations and does not rule out the presence of other *EGFR* or *ERBB2* mutations that may be present but not detected by this assay and which may affect treatment response.

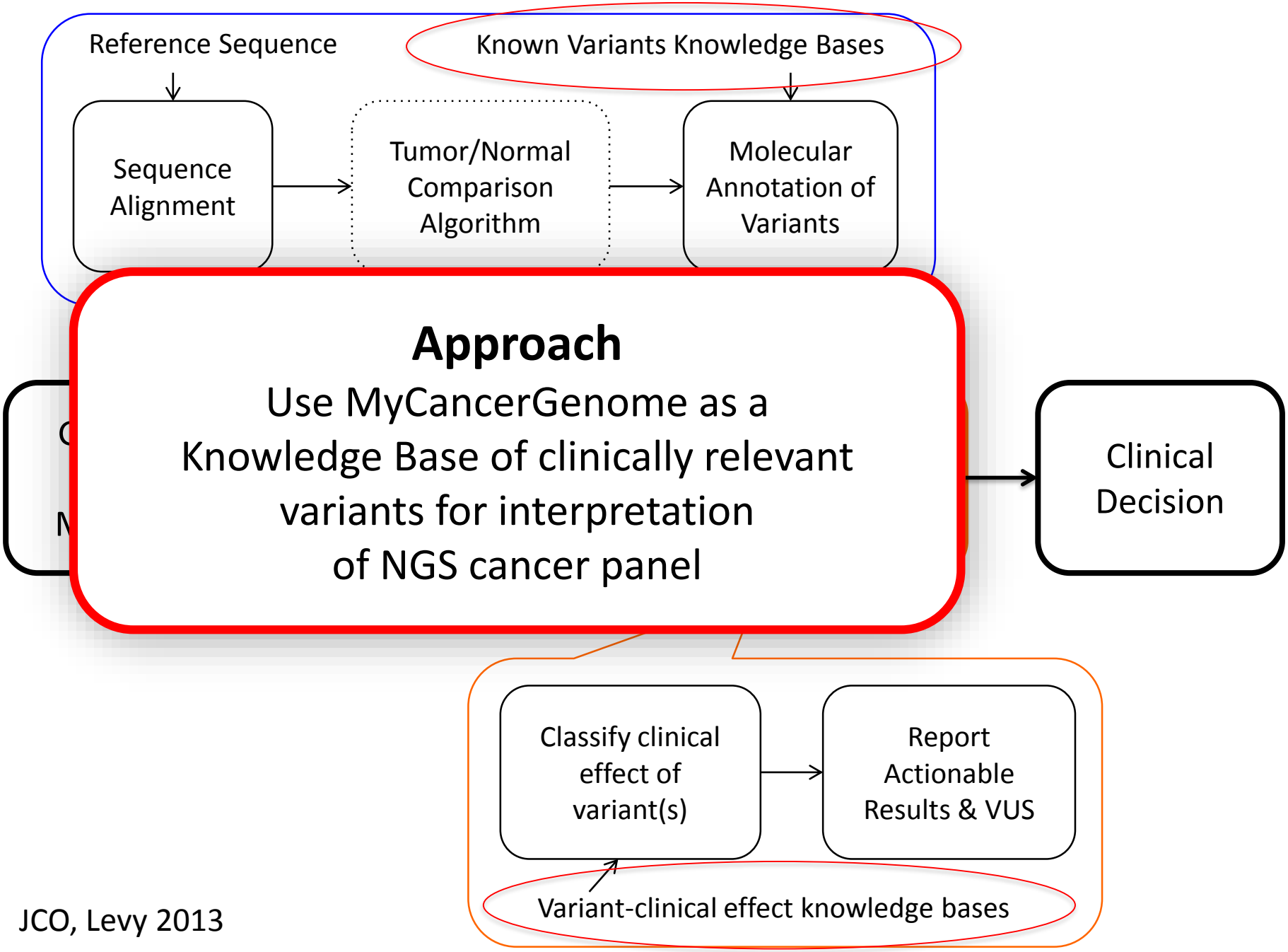
40 Variants
6 Genes

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							

1000s Variants
100s Genes

Next Generation Sequencing

Multi-modal testing



JCO, Levy 2013

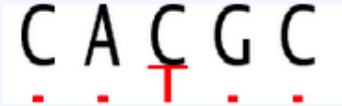
Decision Support for Variant Analysis

Actionable for Tumor Type

Actionable for Other Tumor Type

Not Actionable

QC Metrics | **Actionable for Tumor Type** | Actionable Other | Non-Actionable | Clinical Trials | Patient | REPORT

Variant Info	Ref:Alt	PGM Info	PGM Alignment (Click for BAM Pileup)	PGM Call	PGM Decisio
Count: 0 Total (0 Confirmed) See More Information					
Gene: EGFR Position: 7:55249071-55249071 G Change: c.2369C>T AA Change: T790M Mutation Type: Substitution - Missense Count: 0 Total (0 Confirmed) See More Information	C:T	Total Reads: 500 Variant Reads: 401 VAF: 0.802 QUAL: 100 Q Score: (80/80)		Detected	Detected
Gene: EGFR Position: 7:55259515-55259515 G Change: c.2573T>G AA Change: L858R Mutation Type: Substitution - Missense Count: 0 Total (0 Confirmed) See More Information	T:G	Total Reads: 550 Variant Reads: 500 VAF: 0.909 QUAL: 100 Q Score: (80/80)		Detected	Detected

Decision Support for Variant Interpretation & Reporting

Patient Information

Name: Charles F Bingley
DOB: 4/12/75 **Gender:** Male **MRN:** 10101
Pathologic Diagnosis:

Specimen Information

Specimen Type: primary
Collection Date: 11/1/14
Date Received: 11/2/14

NGS RESULTS

Detected Alterations With Therapeutic Implications

Gene	Alteration	Type of Mutation
EGFR	T790M	Substitution - Missense
EGFR	L858R	Substitution - Missense

Genes With Potentially Relevant Targeted Clinical Trials: EGFR

Genes With Other Non-Synonymous Alterations: None

Alterations that Failed Testing: EGFR (L861Q)

Therapeutic Implications of Genomic Analysis, For Patient's Tumor Type - Level 1

Approved Drugs	Variants Detected	Response to Therapy	Condition	Line of Therapy	Level of Evidence
Afatinib	EGFR L858R, EGFR T790M	Acquired resistance	Non-Small Cell Lung Cancer; When resistance mutation occurs secondary to primary sensitizing mutation in EGFR	Metastatic	NCCN
Erlotinib	EGFR L858R, EGFR T790M	Acquired resistance	Non-Small Cell Lung Cancer; When resistance mutation occurs secondary to primary sensitizing mutation in EGFR	Metastatic	NCCN
Gefitinib	EGFR L858R, EGFR T790M	Acquired resistance	Non-Small Cell Lung Cancer; When resistance mutation occurs secondary to primary sensitizing mutation in EGFR	Metastatic	NCCN

Potentially Relevant Targeted Clinical Trials - Level 3 *(see note)*

Trial Title	Conditions	Relevant Genes
Trial of Erlotinib and BKM120 in Patients With Advanced Non Small Cell Lung Cancer Previously Sensitive to Erlotinib (NCT01487265)	Non Small Cell Lung Cancer	EGFR
Phase II AZD9291 Open Label Study in NSCLC After Previous EGFR TKI Therapy in EGFR and T790M Mutation Positive Tumours (NCT02094261)	Non Small Cell Lung Cancer	EGFR
BATTLE-2 Program: A Biomarker-Integrated Targeted Therapy Study (NCT01248247)	Lung Cancer	EGFR
AZD9291 in Combination With Ascending Doses of Novel Therapeutics (NCT02143466)	Advanced Non Small Cell Lung Cancer	EGFR

Decision Support for Variant Interpretation & Reporting

Patient Information

Name: Charles F Bingley
DOB: 4/12/75 **Gender:** Male **MRN:** 10101
Pathologic Diagnosis:

Specimen Information

Specimen Type: primary
Collection Date: 11/1/14
Date Received: 11/2/14

NGS RESULTS

Detected Alterations With Therapeutic Implications *(see details in the follo*

Gene	Alteration	Type of Mutation
EGFR	T790M	Substitution - Missense
EGFR	L858R	

Variants with Potential Clinical Utility

Drug Sensitivity
In Disease (Level 1)
In Other Disease (Level 2)

Therapeutic Implications of Genomic Analysis, For Patient's Tumor Type - Level 1 *(see note)*

Approved Drugs	Variants Detected	Response to Therapy	Condition	Line of Therapy	Level of Evidence
Afatinib	EGFR L858R, EGFR T790M	Acquired resistance	Non-Small Cell Lung Cancer; When resistance mutation occurs secondary to primary sensitizing mutation in EGFR	Metastatic	NCCN
Erlotinib	EGFR L858R, EGFR T790M	Acquired resistance	Non-Small Cell Lung Cancer; When resistance mutation occurs secondary to primary sensitizing mutation in EGFR	Metastatic	NCCN
Gefitinib	EGFR L858R, EGFR T790M	Acquired resistance	Non-Small Cell Lung Cancer; When resistance mutation occurs secondary to primary sensitizing mutation in EGFR	Metastatic	NCCN

AZD9291 in Combination With Ascending Doses of Novel Therapeutics (NCT02143466)	Advanced Non Small Cell Lung Cancer	EGFR

Decision Support for Variant Interpretation & Reporting

Patient Information

Name: Charles F Bingley
DOB: 4/12/75 **Gender:** Male **MRN:** 10101
Pathologic Diagnosis:

Specimen Information

Specimen Type: primary
Collection Date: 11/1/14
Date Received: 11/2/14

NGS RESULTS

Detected Alterations With Therapeutic Implications *(see table legend)*

Gene	Alteration	Type of Mutation
EGFR	T790M	Substitution - Missense
EGFR	L858R	Substitution - Missense

Genes With Potentially Relevant Targeted Clinical Trials: EGFR

Genes With Other Non-Synonymous Alterations: None

Alterations that Failed Testing: EGFR (L861Q)

Potential Clinical Trials (Level 3)

Therapeutic Implications of Genomic Analysis, For Patient's Tumor Type - Level 1 *(see note)*

Approved Drugs	Variants Detected	Response to Therapy	Condition	Line of Therapy	Lev Evid
Afatinib	EGFR L858R,	Acquired	Non-Small Cell Lung Cancer; When resistance mutation occurs	Metastatic	NCCN

Potentially Relevant Targeted Clinical Trials - Level 3 *(see note)*

Trial Title	Conditions	Relevant Genes
Trial of Erlotinib and BKM120 in Patients With Advanced Non Small Cell Lung Cancer Previously Sensitive to Erlotinib (NCT01487265)	Non Small Cell Lung Cancer	EGFR
Phase II AZD9291 Open Label Study in NSCLC After Previous EGFR TKI Therapy in EGFR and T790M Mutation Positive Tumours (NCT02094261)	Non Small Cell Lung Cancer	EGFR
BATTLE-2 Program: A Biomarker-Integrated Targeted Therapy Study (NCT01248247)	Lung Cancer	EGFR
AZD9291 in Combination With Ascending Doses of Novel Therapeutics (NCT02143466)	Advanced Non Small Cell Lung Cancer	EGFR

Detailed Summary of Alteration In Disease

Detected Alterations With Therapeutic Implications in Patient's Tumor Type - Level 1 *(see note)*

Gene: EGFR **Nucleotide:** c.2369C>T **Condition:** Non-Small Cell Lung Cancer

Alteration Detected: T790M **Variation Type:** Substitution - Missense

About this Gene

EGFR (epidermal growth factor receptor, also known as ERBB1 and HER1) is a gene that encodes for the epidermal growth factor receptor protein. Missense mutations, deletions, and insertions are observed in cancers such as lung cancer and glioblastoma. Activating EGFR mutations increase the kinase activity of EGFR, leading to hyperactivation of downstream pro-survival signaling pathways (Sordella et al. 2004).

Pathways

Receptor tyrosine kinase

Mutation Location in Gene and/or Protein

Kinase domain (exon 20)

Mutation Prevalence

Frequency of EGFR mutations in NSCLC: 10% in the USA and 35% in Asia (Lynch et a

Frequency of T790M mutations in EGFR-mutated NSCLC: < 5% of untreated EGFR mutant tumors (Inukai et al. 2006); 50% of EGFR mutant tumors with acquired resistance to erlotinib/gefitinib (Kobayashi et al. 2005; Pao et al. 2005)

Response to Drugs

Response to anti-EGFR antibodies: Currently no role for EGFR mutation in predicting response in NSCLC
Response to anti-EGFR antibodies: Currently no role for EGFR mutation in predicting response in NSCLC
Response to EGFR TKIs: Confers decreased sensitivity

Reference

http://www.mycancergenome.org/content/disease/lung-cancer/egfr/4

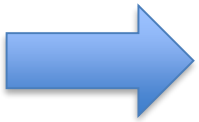
Content from
My Cancer Genome

Link to
MyCancerGenome.org

Trial Matching Decision Support

NCI Match
21 trial arms

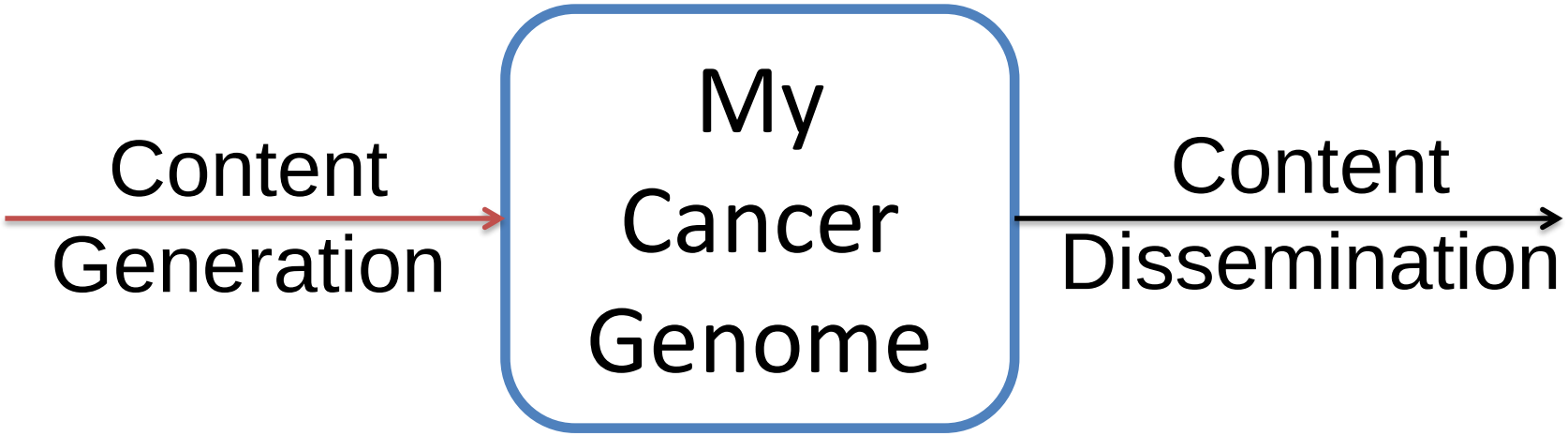
861 cases with NGS testing at Vanderbilt



36% potential match

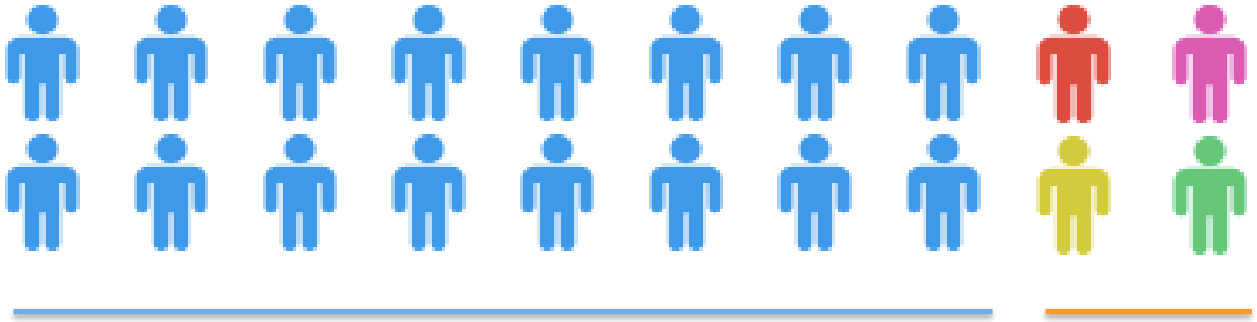
Next Steps: Extend trial annotation
& integrate algorithm into clinical workflow

Challenges & Future Directions



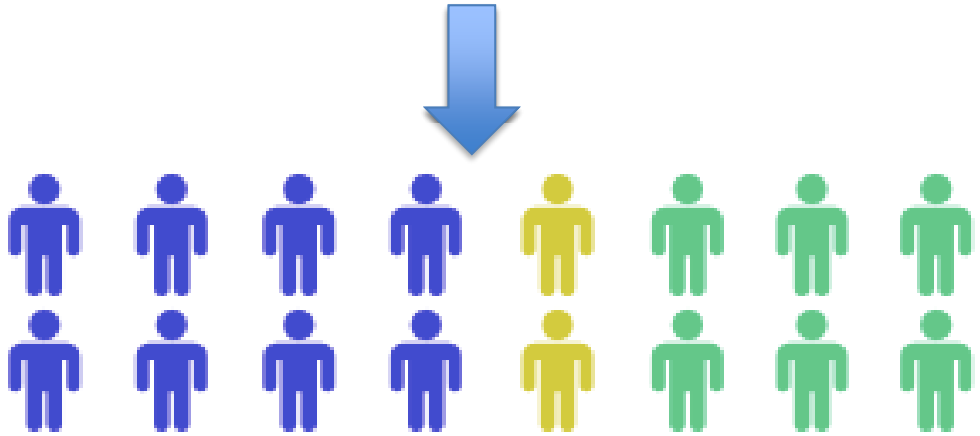
Small Sub-populations

Targeted Therapy



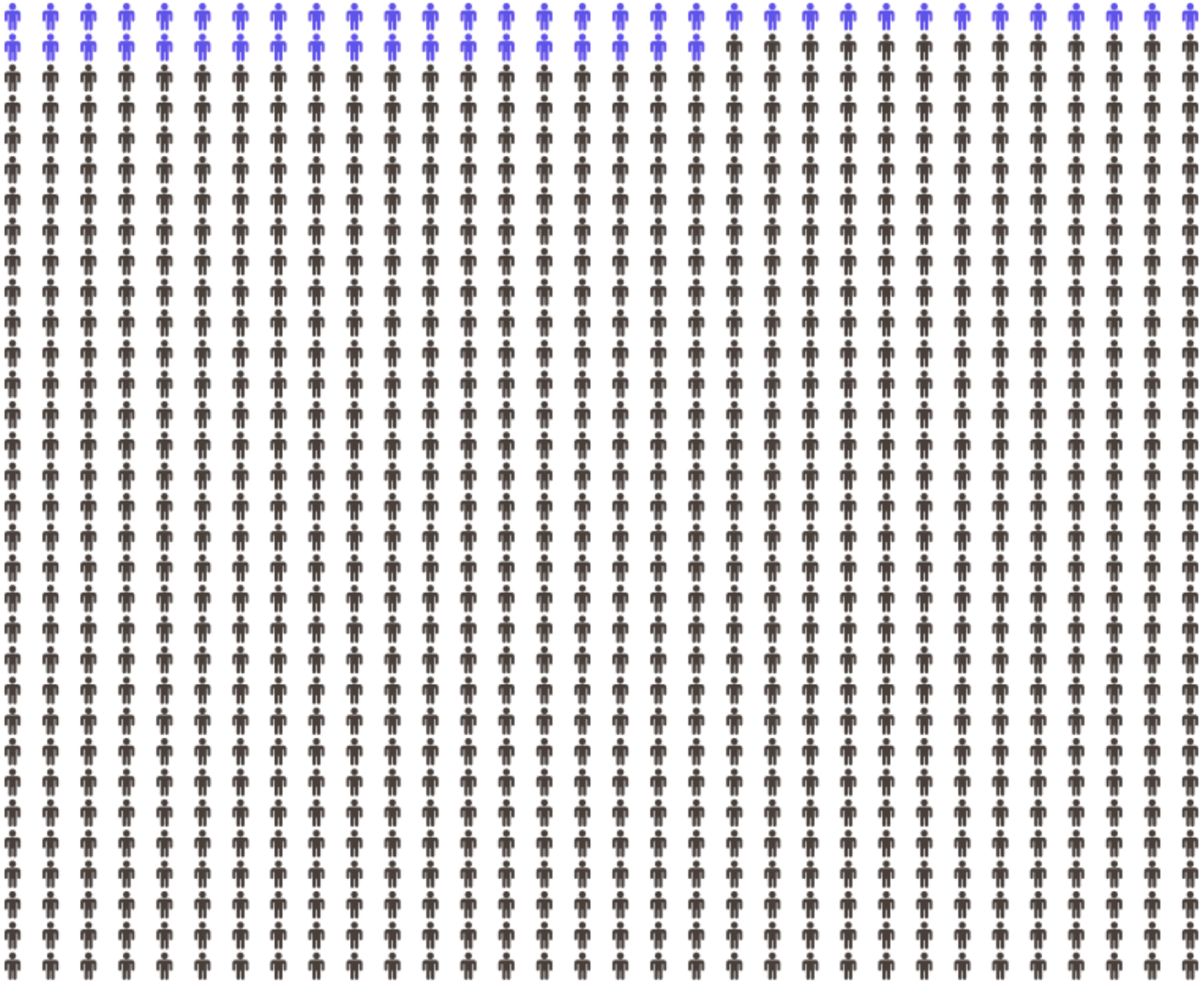
Primary Sensitivity

Primary Resistance

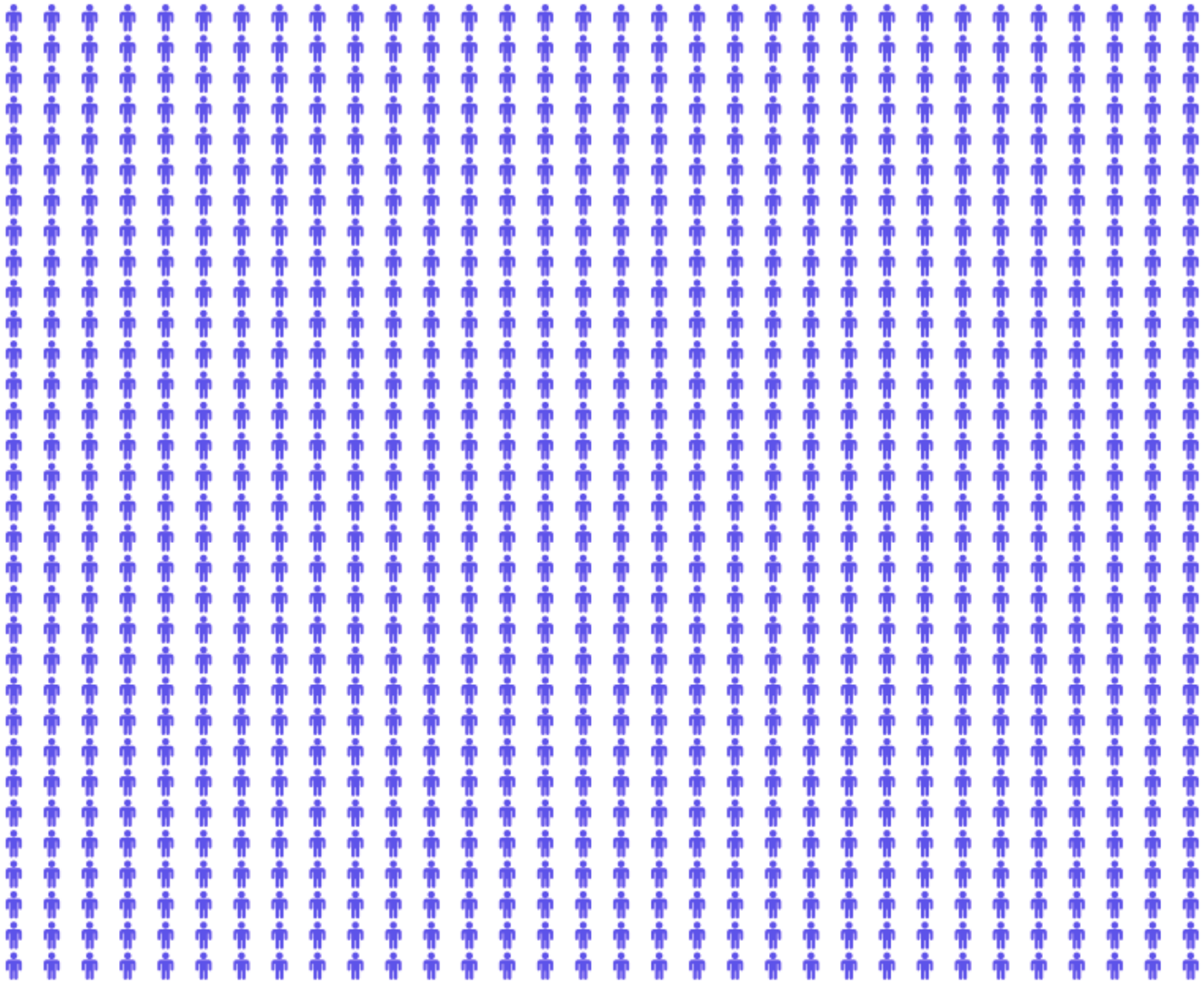


Acquired Resistance

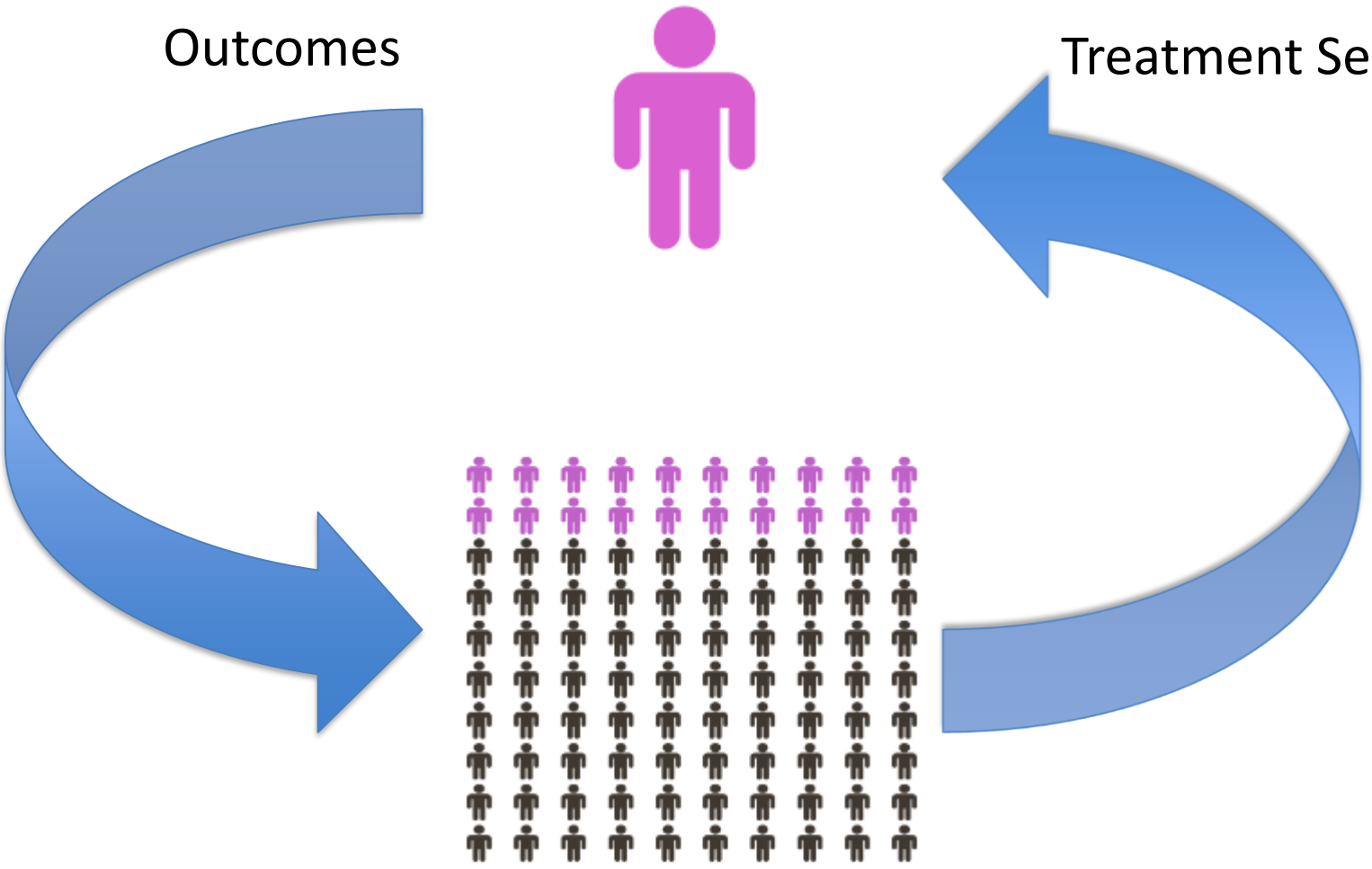
Only 5% of cancer patients participate in clinical trials



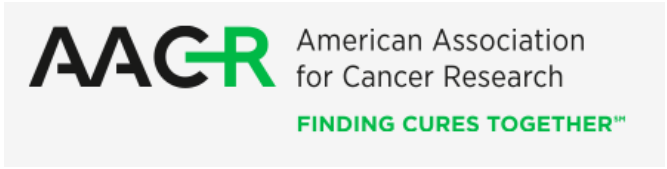
Learning Cancer System



Learning Cancer System



Many Are Looking at Different Parts of the Same Problem



President Obama's State of the Union Address pushes for precision medicine

- 2015 – 1 Million person precision medicine cohort
- 2016 – Moonshot to "cure" cancer (Biden named "Cancer Czar"

Evolution of Clinical Decision Support

Evidence Driven

Protocol Driven

Pathway Driven

Data Driven?

Summary

- Rise of genomic profiling in cancer
- My Cancer Genome knowledge base provides decision support for clinical utility of alterations in cancer
- Strategies for content generation and dissemination
- Strategies for clinical decision support

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MCG Contributors
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mia.levy@vanderbilt.edu