Individualized Cancer Therapy: Chemotherapy Resistance Testing before Therapy

1st International Oncological Conference

Wrocław, October 6th, 2012

Dr. Frank Kischkel

Individualized Cancer Therapy:
Drug Treatment
Testing before Therapy

1st International Oncological Conference

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Therapy Select

Individualized Cancer Therapy:
Drug Treatment
Testing before Therapy

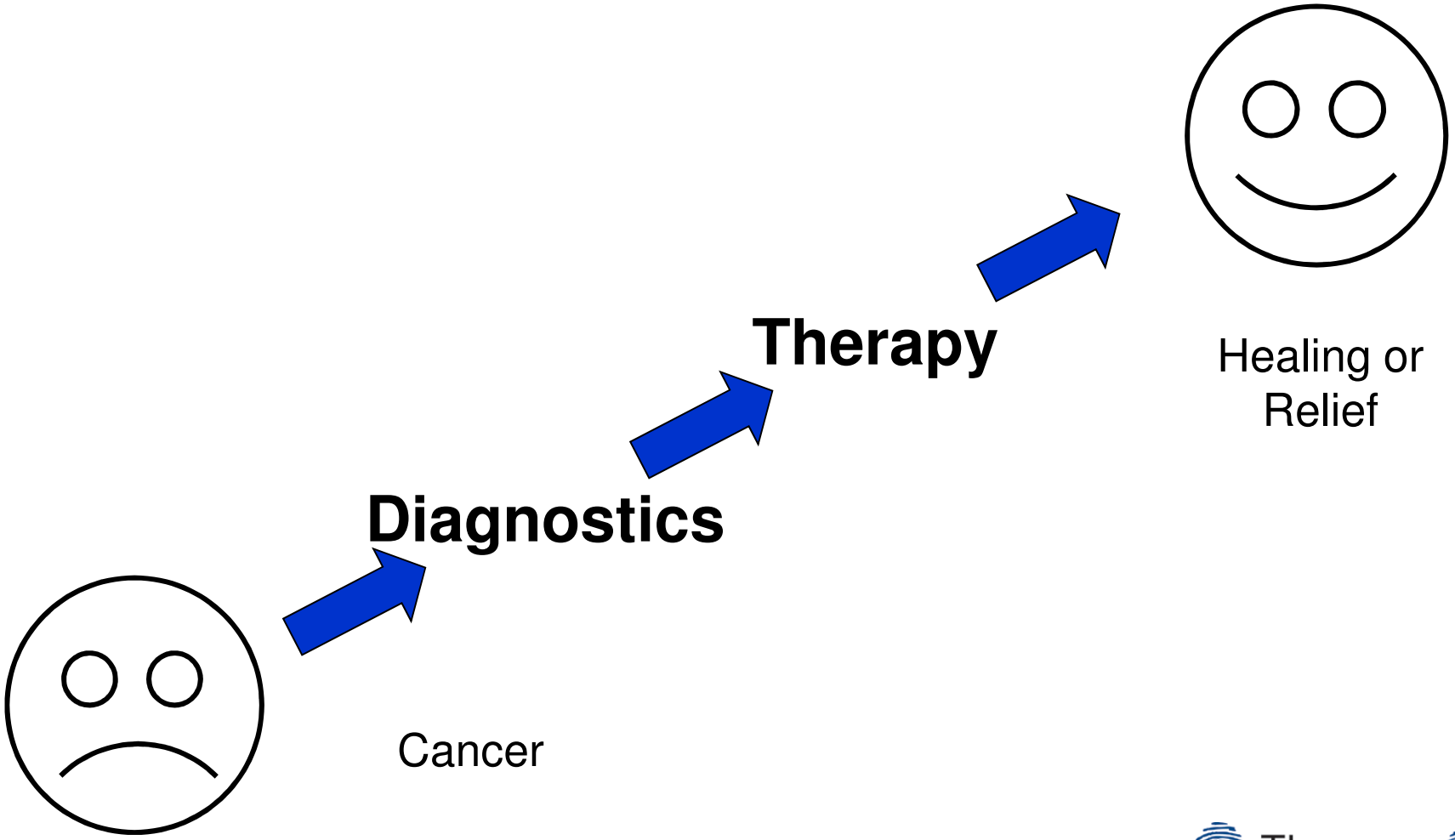
CTR-Test®

Chemotherapy-Resistance-Test

ONCOMPASS

Cancer Diagnostics

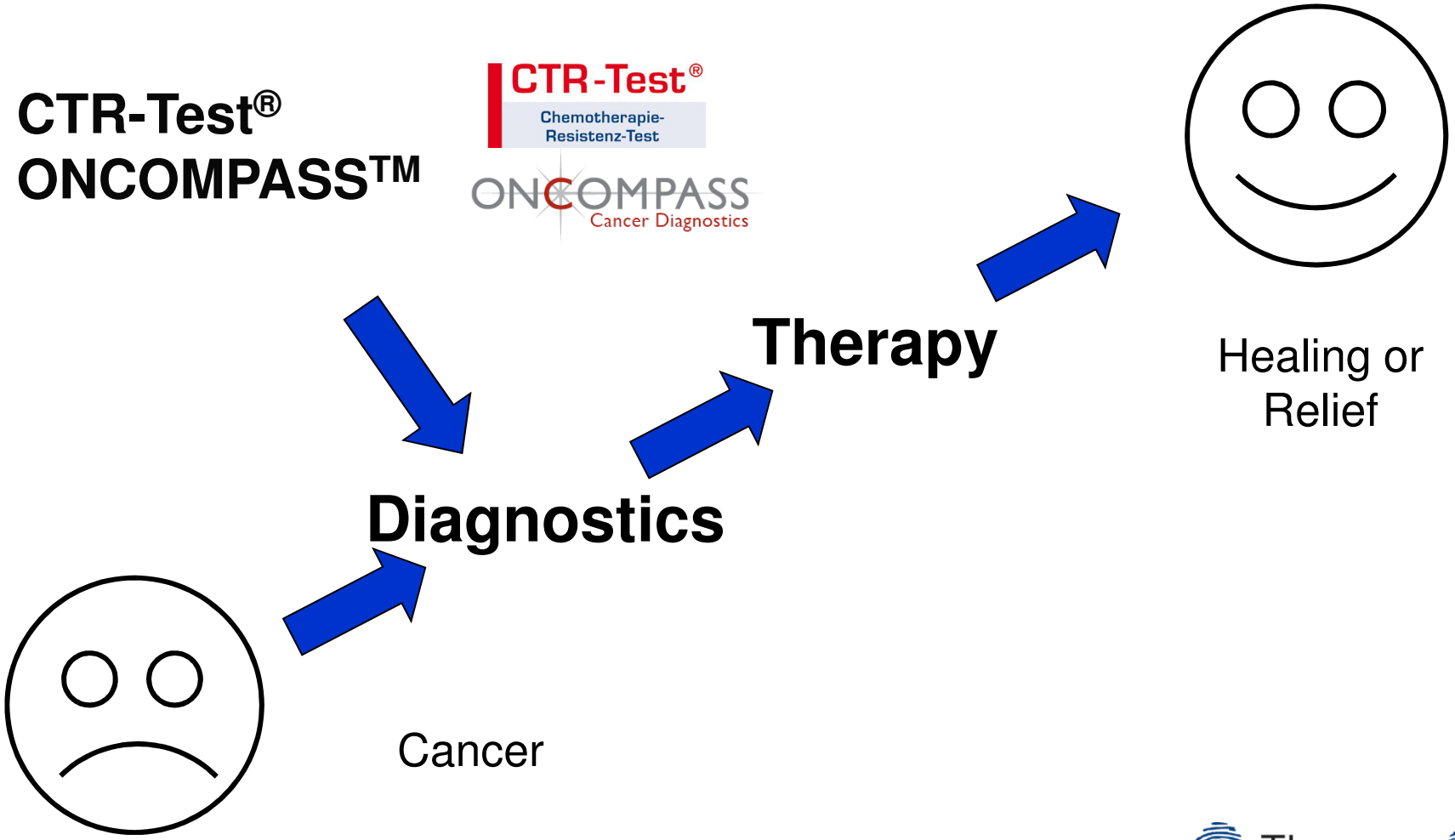
Individualized Cancer Therapy



Therapy Select

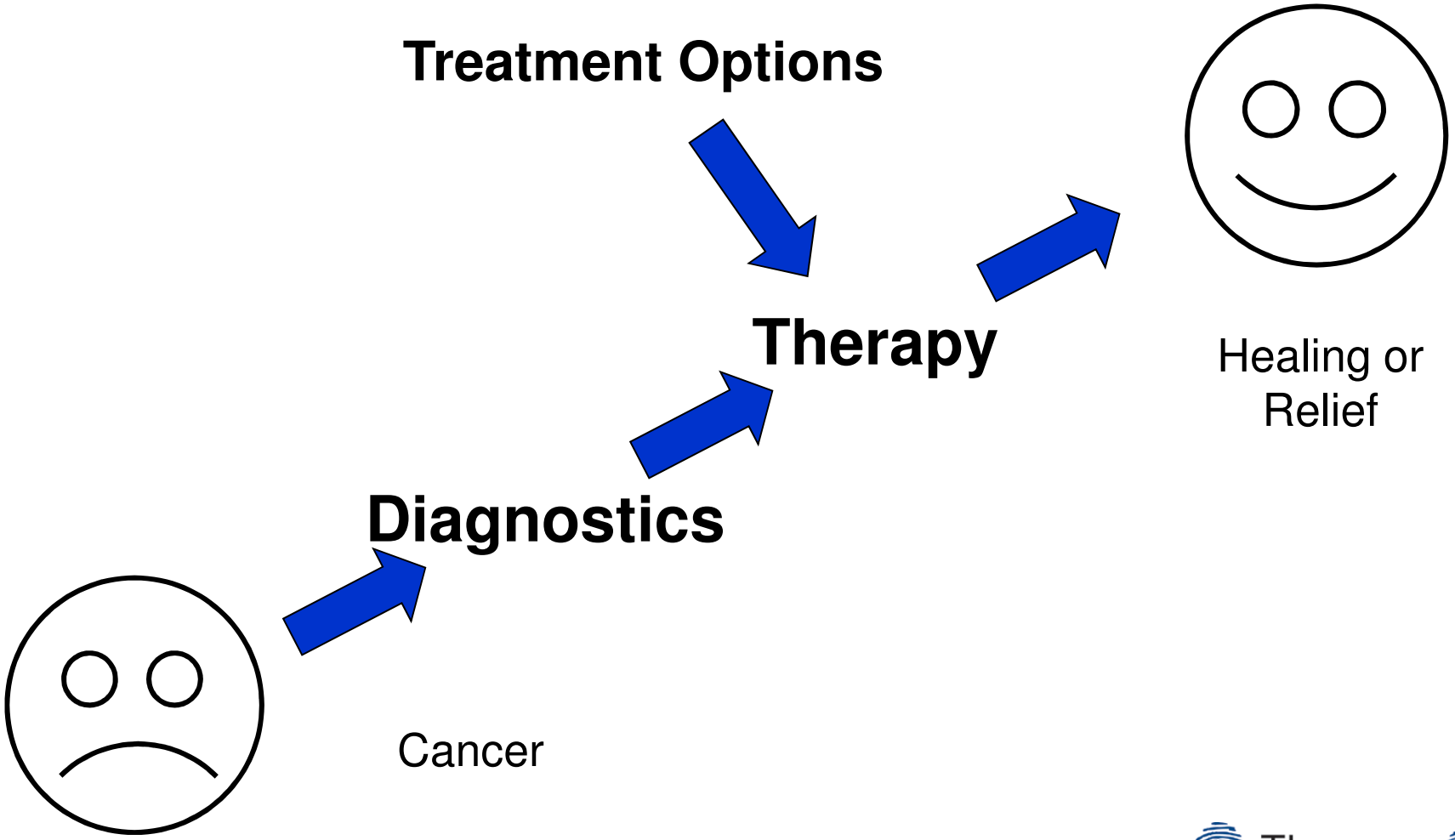
Individualized Cancer Therapy

CTR-Test®
ONCOMPASS™



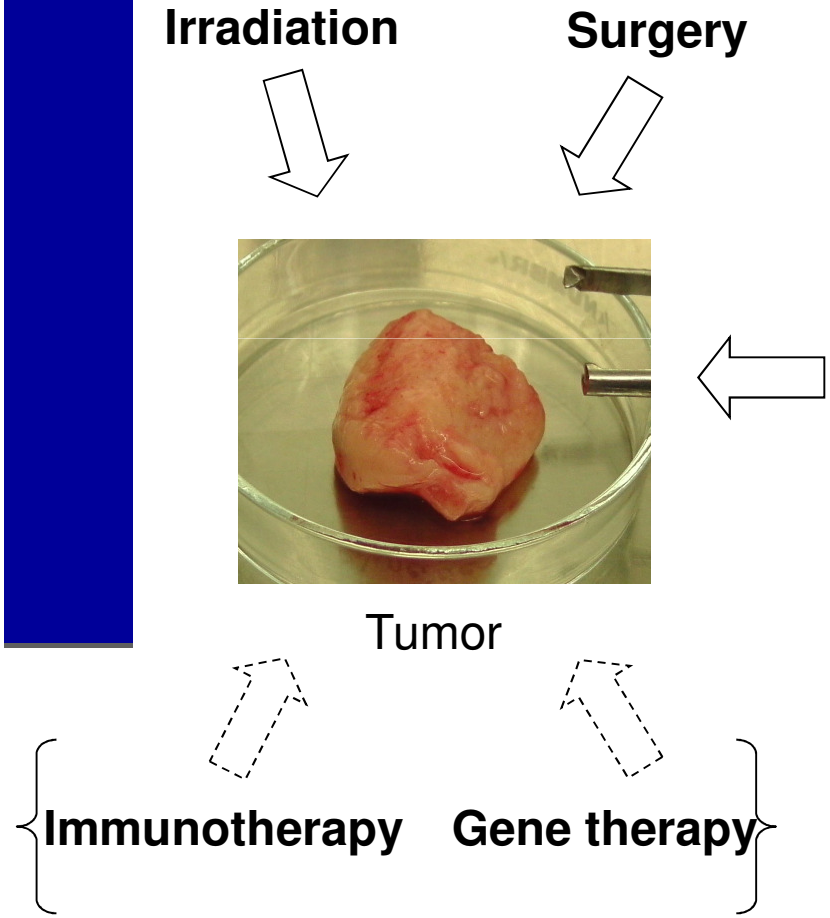
Therapy Select

Individualized Cancer Therapy



Therapy Select

Treatment Options for Cancer



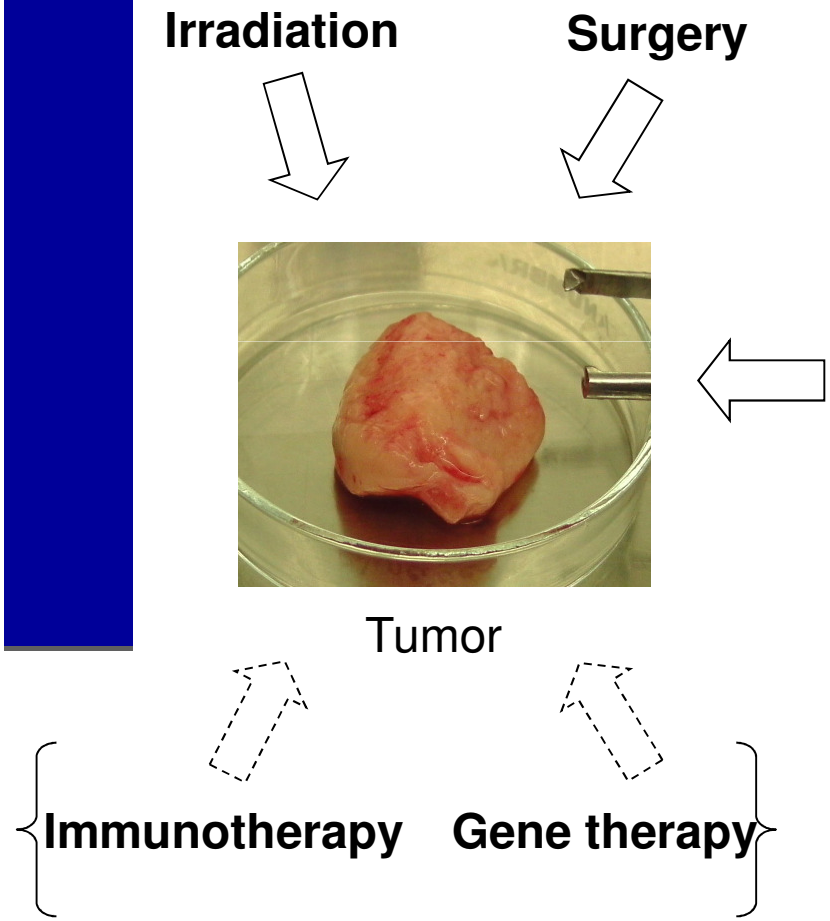
Medication

Type	Action	Target
Chemotherapeutic drugs	Cell division	TC
Hormones	Cell division	TC
Inhibitors of signal transduction	Inside (Tumor) cells	TZ, VZ
Antibodies (monoclonal)	Outside (Tumor) cells	TC, VC, IC
Zytokines	Immuno-modulation	IC

TC … Tumor cells; VC … Vascular cells; IC … Cells of the immune system

Therapy Select

Treatment Options for Cancer



Medication

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Zytokines	Immuno-modulation	IC

TC … Tumor cells; VC … Vascular cells; IC … Cells of the immune system

Therapy Select

CTR-Test® can evaluate all drugs that act against cancer cells directly

CTR-Test®
Chemotherapie-Resistenz-Test

Medication

Type	Action	Target
Chemotherapeutic drugs	**Cell division**	**TC**
Hormones	**Cell division**	**TC**
Inhibitors of signal transduction	**Inside (Tumor) cells**	**TZ**, VZ
Antibodies (monoclonal)	**Outside (Tumor) cells**	**TC**, VC, IC
Zytokines	Immuno-modulation	IC

TC … Tumor cells; VC … Vascular cells; IC … Cells of the immune system

Therapy Select

ONCOMPASS Can Evaluate All Targeted Drugs

Medication

Type	Action	Target
Chemotherapeutic drugs	**Cell division**	**TC**
Hormones	**Cell division**	**TC**
Inhibitors of signal transduction	**Inside (Tumor) cells**	**TZ**, VZ
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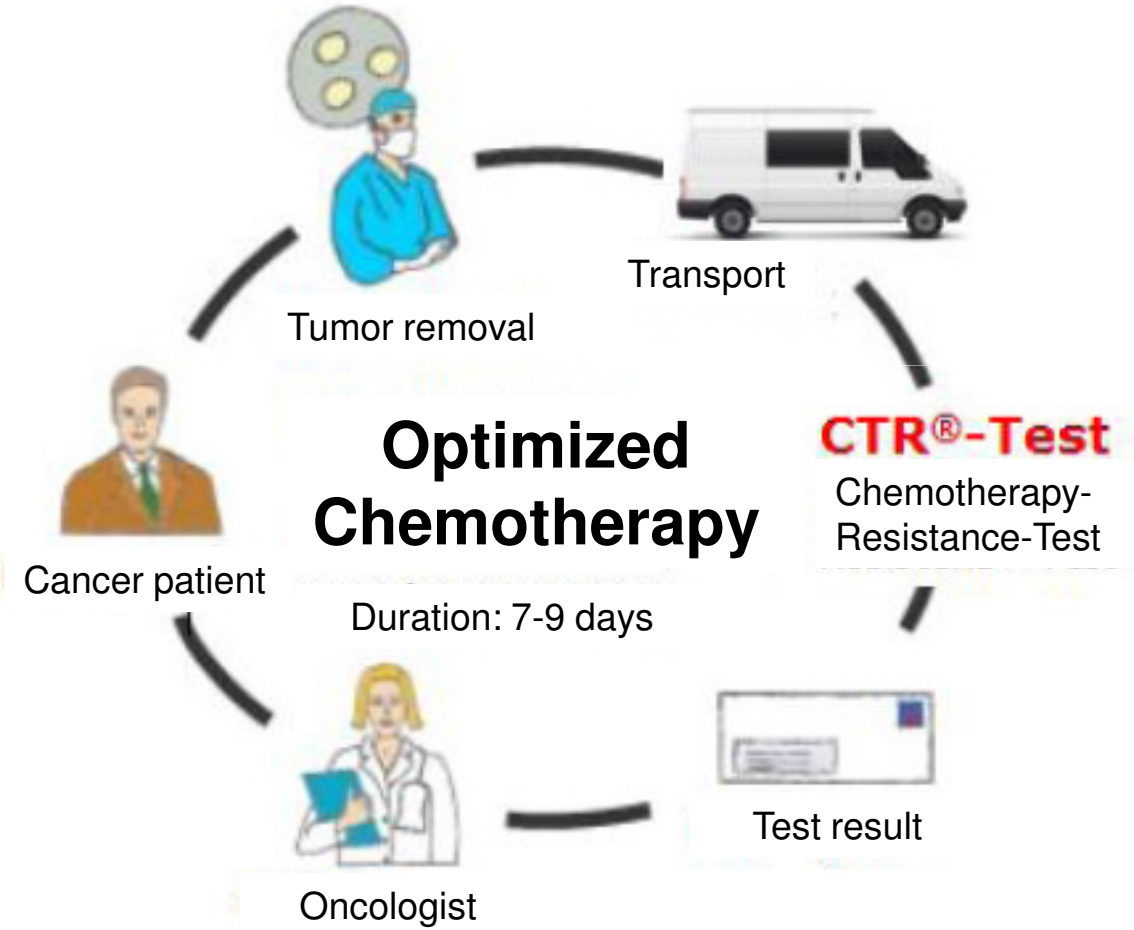
TC … Tumor cells; VC … Vascular cells; IC … Cells of the immune system

Chemotherapy-Resistance-Test

CTR-Test®

Therapy Select

The Logistic Chain



Therapy Select

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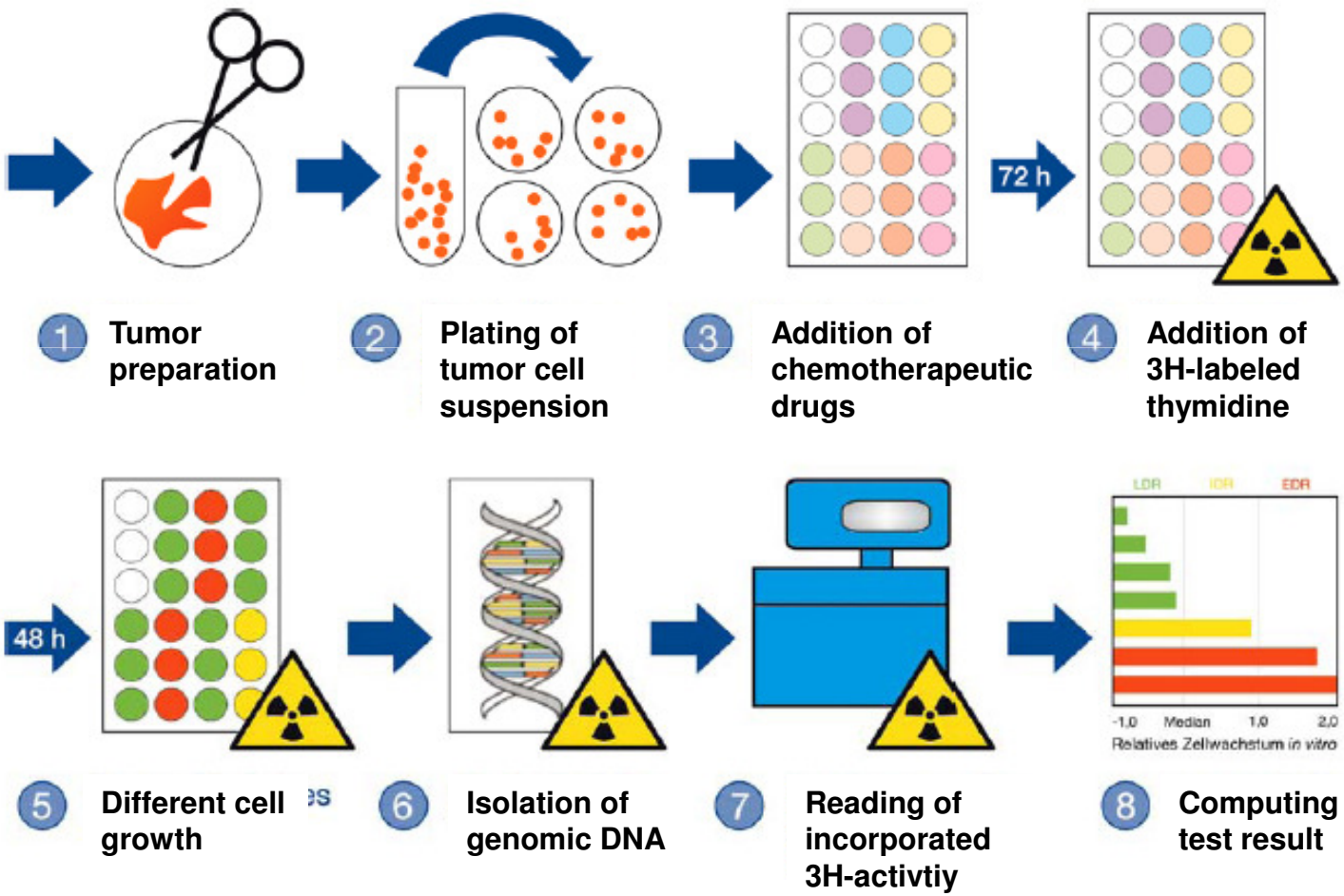
The Procedure

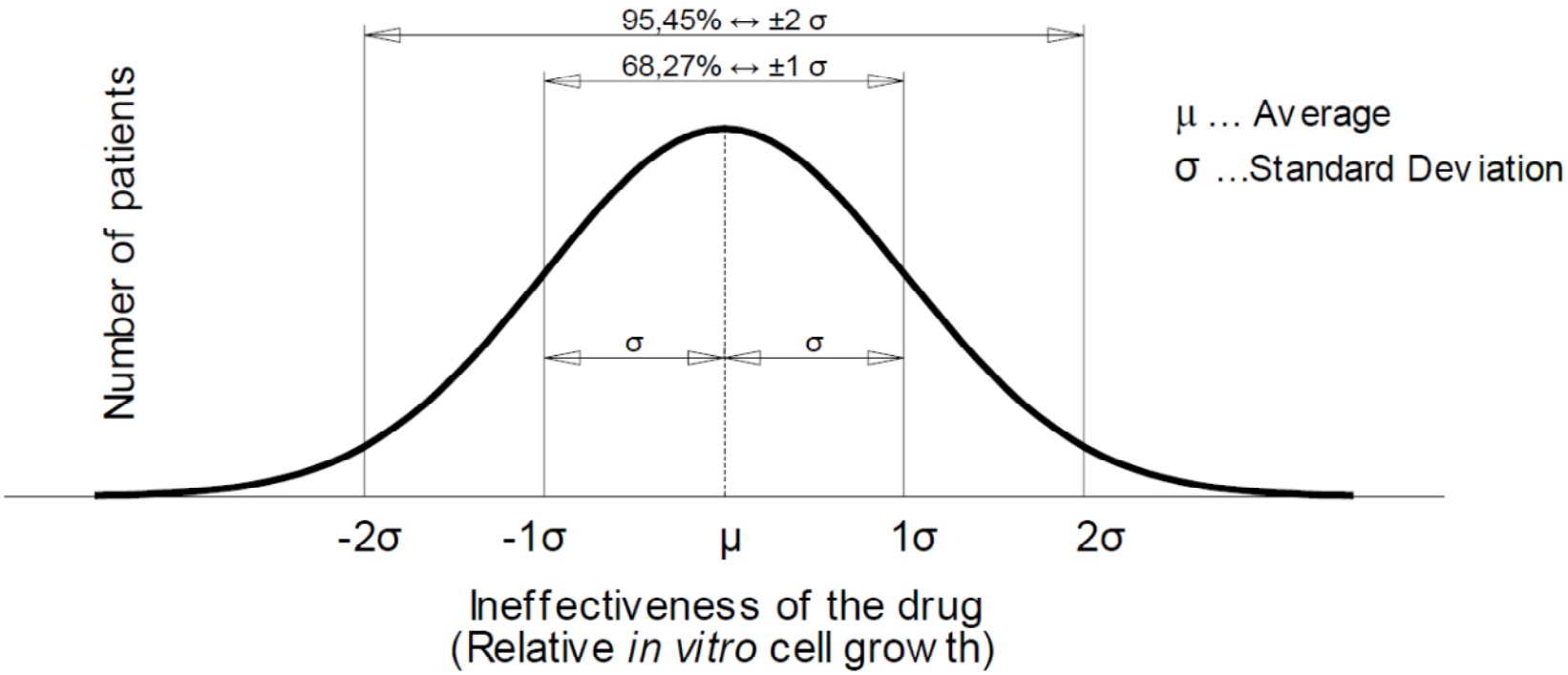


1. Tumor preparation
2. Plating of tumor cell suspension
3. Addition of chemotherapeutic drugs
4. Addition of 3H-labeled thymidine
5. Different cell growth
6. Isolation of genomic DNA
7. Reading of incorporated 3H-activtiy
8. Computing test result

Therapy Select

The Test Report

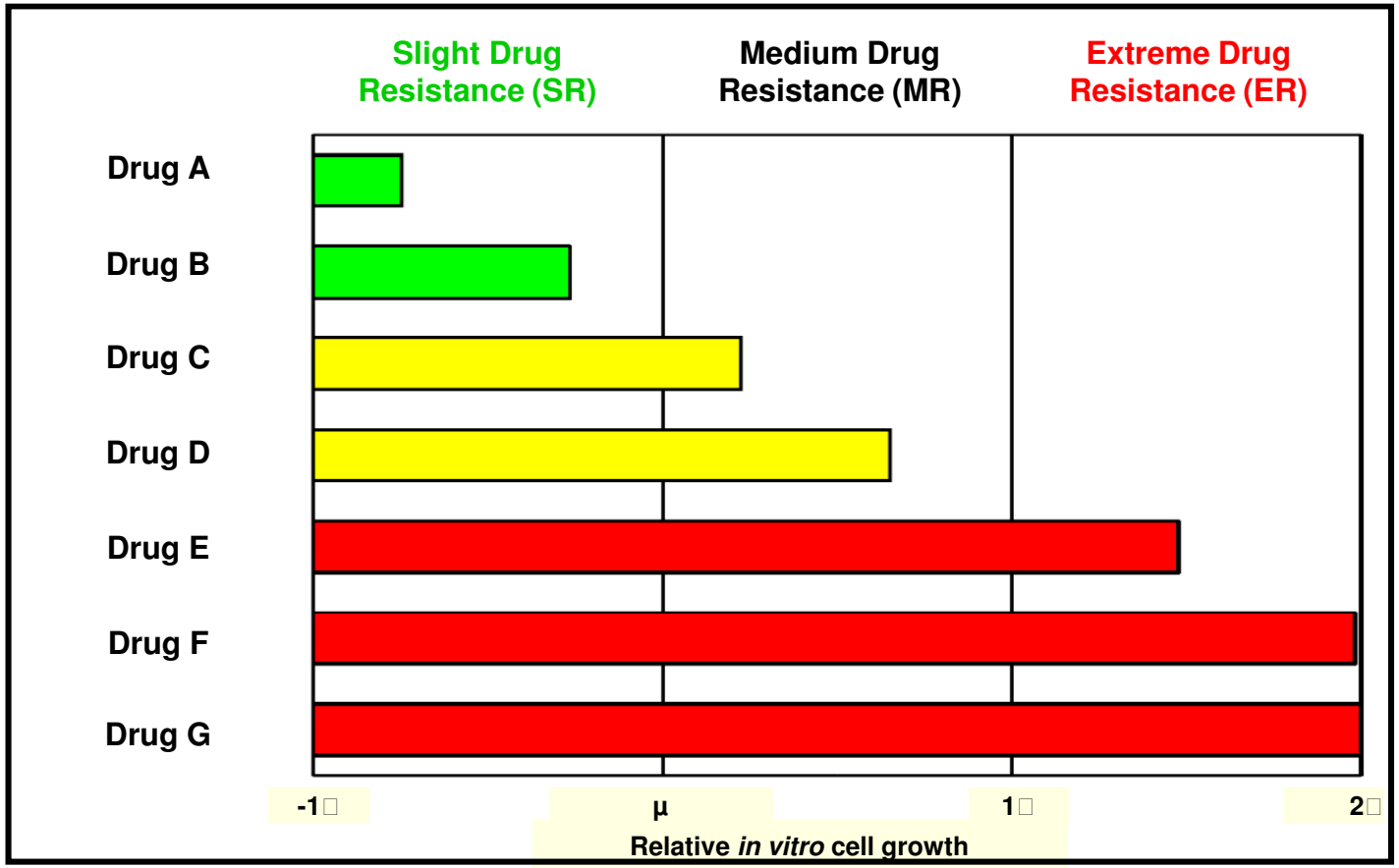
Standard distribution of a drug effect



Therapy Select

CTR-Test®

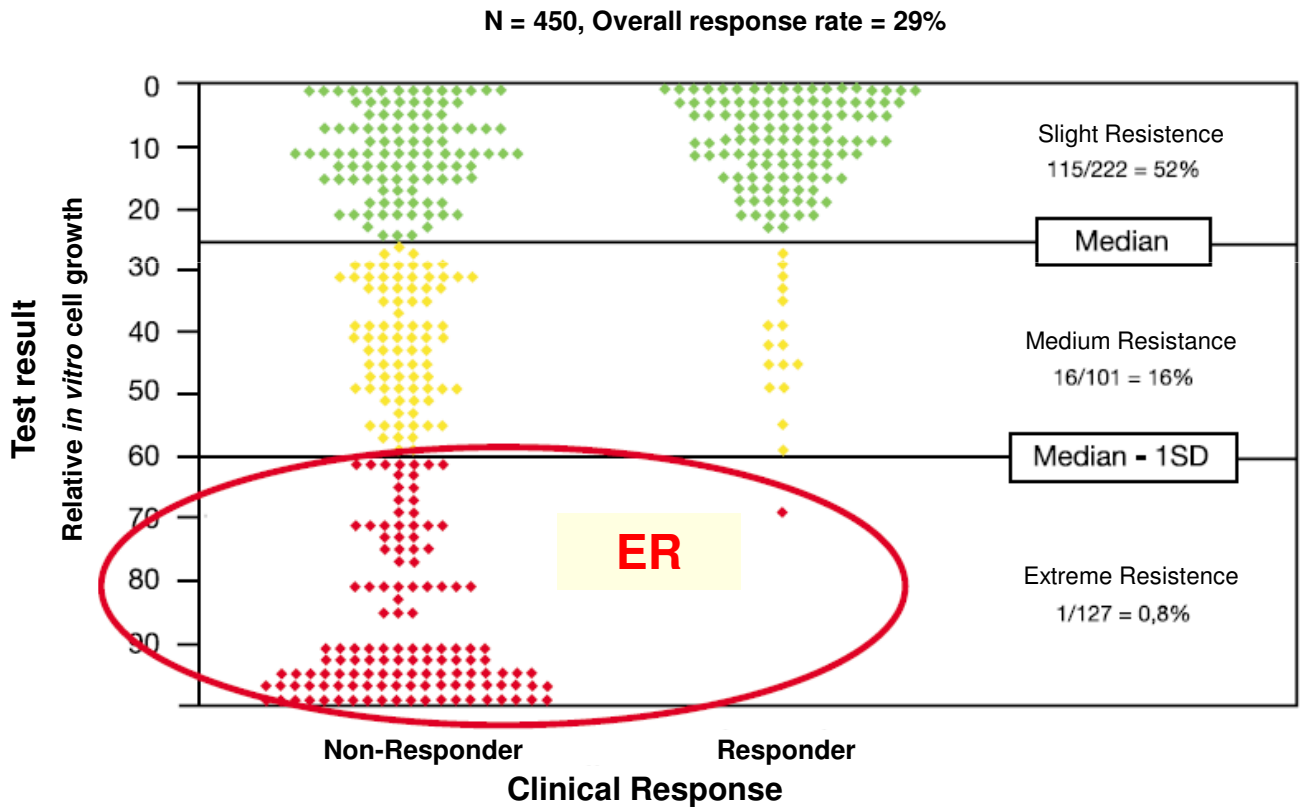
The Test Report



Therapy Select

CTR-Test®

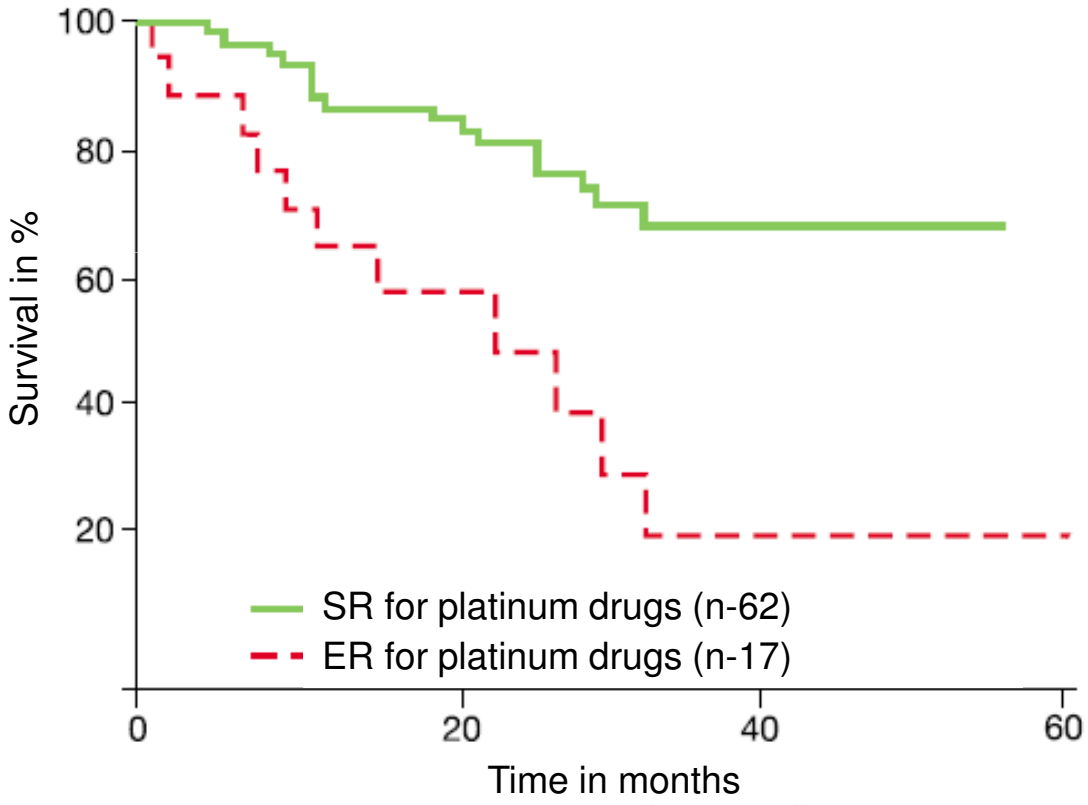
Correlation of CTR-Test® Result and Clinical Response



Kern DH, Weisenthal LM (1990) J Natl Cancer Inst. 82(7):582-8

Therapy Select

Correlation of CTR®-Test Result and Overall Survival



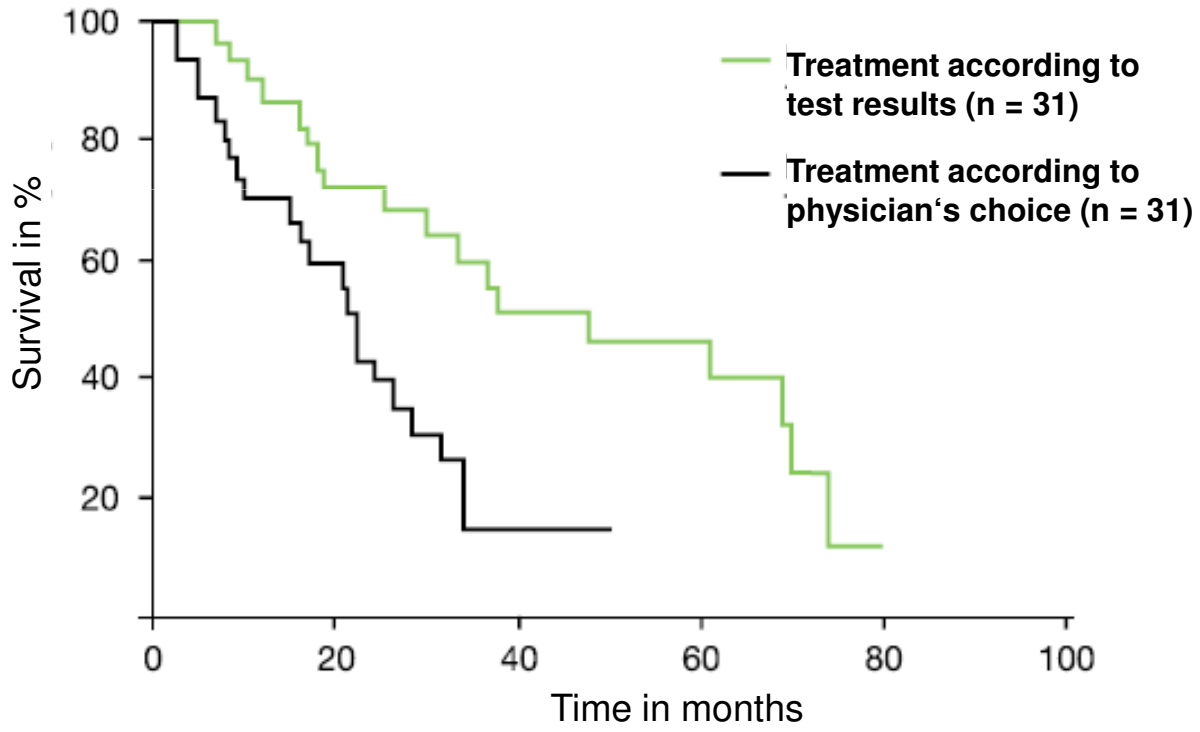
Holloway et al. (2002) Gynecologic Oncology 87(1):8-16

Therapy Select

CTR-Test®

Extended Survival by Treatment According to Test Result

- Ovarian cancer, platinum-sensitive group



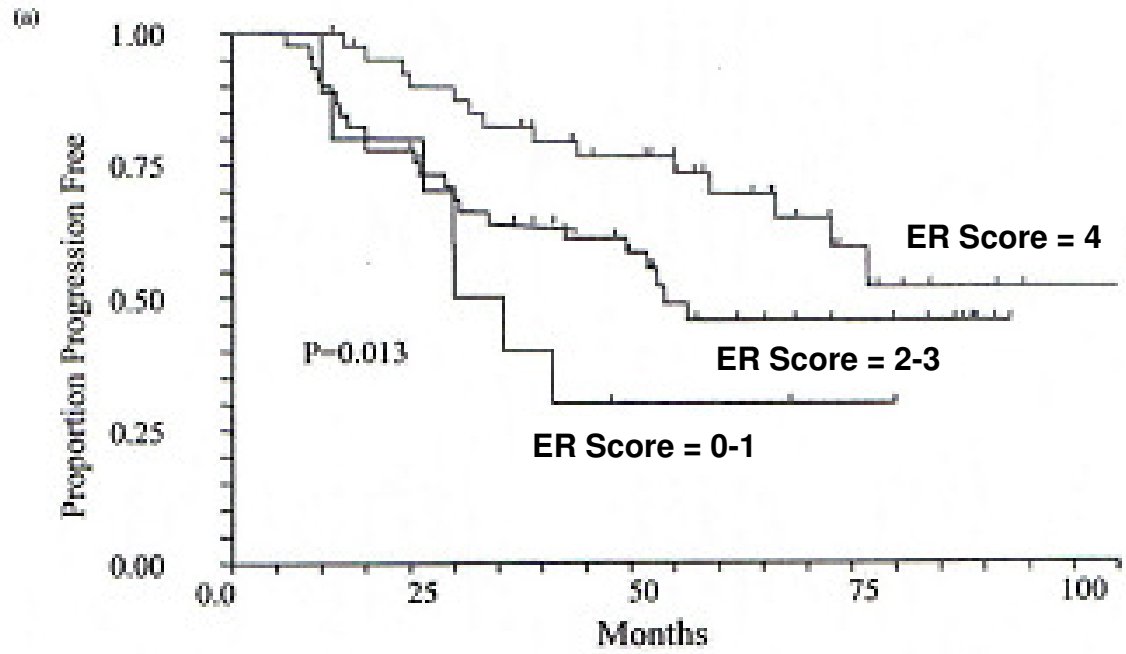
Loizzi et al. (2003) Am J Obstet Gynecol 189(5): 1301-1307

Therapy Select

CTR-Test®

Best Drug Combination Correlates with Single Active Drugs

- Kaplan-Meier progression free survival curves for patients with ER scores of 4 vs. 2-3 vs. 0-1.



Mehta RS et al. (2001) Breast Cancer Research and Treatmant 66(3): 225-237.

Therapy Select

ONCOMPASS

Cancer Diagnostics

KPS DIAGNOSTICS GmbH

KPS

Therapy Select

MOLECULAR ONCOLOGY REVOLUTION

NOVEMBER 2011

ASCO

American Society of Clinical Oncology

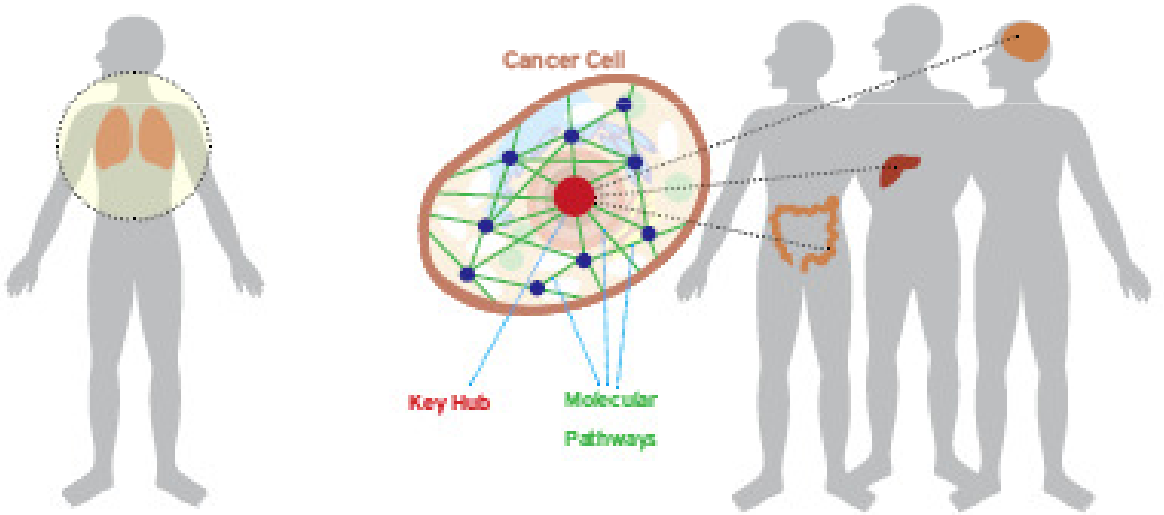
ACCELERATING PROGRESS AGAINST CANCER

ASCO's Blueprint for Transforming Clinical and Translational Cancer Research

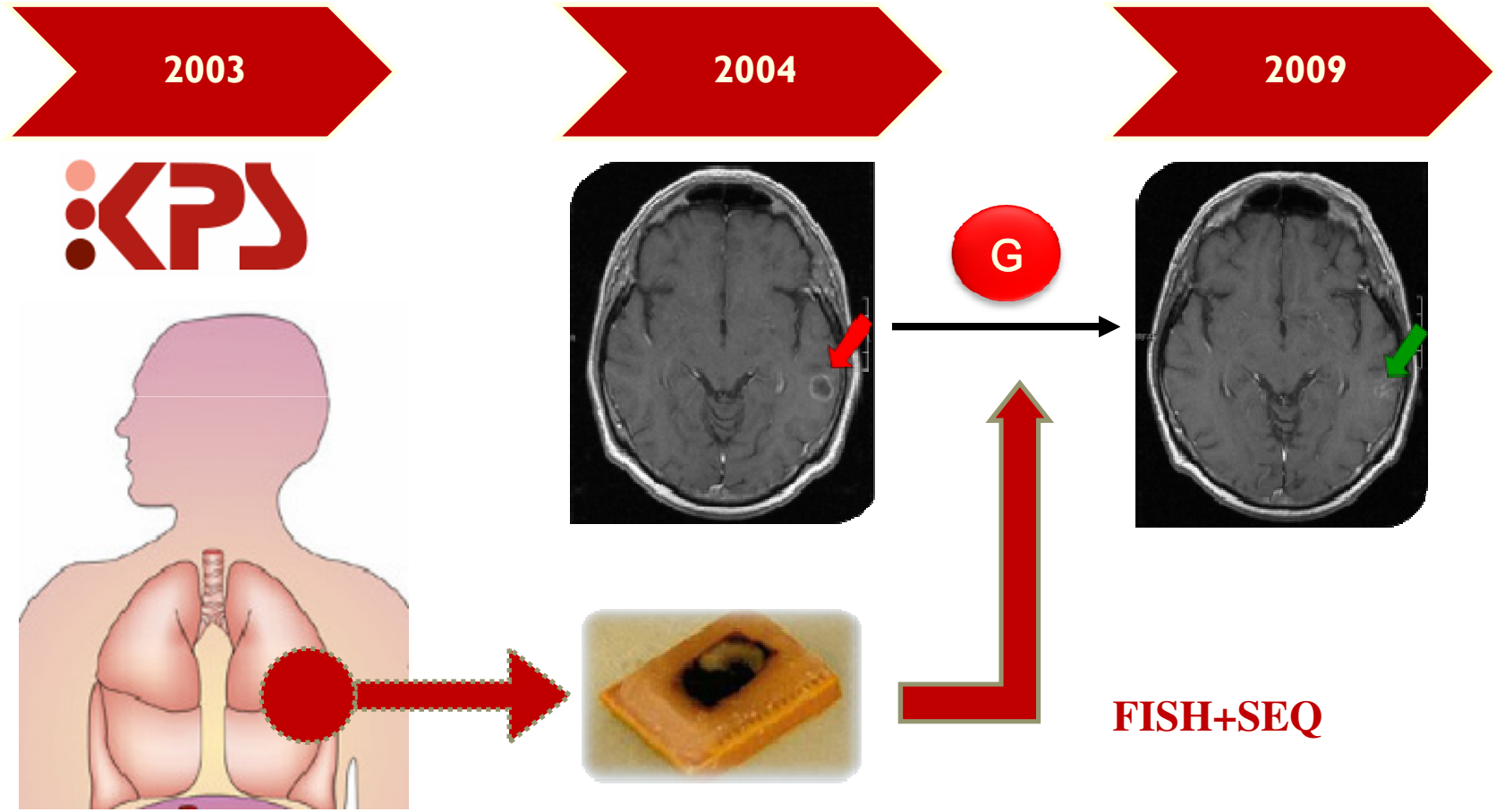
A New Model for Therapeutic Development

OLD MODEL: Treatment is determined by a tumor's location in the body, without regard to the molecular characteristics of the patient or the tumor.

NEW MODEL: Treatment is determined by key molecular "hubs" that must be targeted within the cells, and is only administered to patients whose tumors are found to have those hubs – potentially without regard to the tumor's location in the body.



FIRST PROSPECTIVE TREATMENT OF A EGFR MUTANT NSCLC PATIENT



Modern treatment of lung cancer: case 1. Amplification and mutation of the epidermal growth factor receptor in metastatic lung cancer with remission from gefitinib. Schwab R, Pinter F, Moldavy J, Papay J, Strausz J, Kopper L, Keri G, Pap A, Petak I, Oreskovich K, Mangel L. J Clin Oncol. 2005 Oct 20;23(30):7736-8.

RESPONSE TO EGFR INIBITORS IS INDEPENDENT FROM EGFR IHC

Ana-lyis	Case	Tissue-Sample	Age	Gen.	Smoker	EGFR TK mutation	TKI	Clinical Response
Retrosp	Rtr 1	ADC	58	Fem.	Never	del747-753insS	gefitinib	**CR**
	Rtr 2	ADC	68	Fem.	Never	del746-750	erlotinib	**CR**
	Rtr 3	adsq. c.	62	Fem.	Smoker	L858R	erlotinib	**CR**
	Rtr 4	ADC	66	Fem.	Never	del746-750	erlotinib	PR
	Rtr 5	ADC	50	Male	Never	del746-751insA	erlotinib	PR
	Rtr 6	ADC	65	Fem.	Never	L858R	erlotinib	PR
	Rtr 7	ADC	72	Fem.	Never	del746-750	erlotinib	PR
	Rtr 8	anap. c.	54	Male	Smoker	del746-750*	erlotinib	SD
Prospektív	Pr 1	ADC	61	Fem.	Never	del747-750insP	gefitinib	**CR**
	Pr 2	ADC	45	Fem.	Never	del746-752insV	gefitinib	**CR**
	Pr 3	ADC	50	Male	Smoker	del747-753insS	erlotinib	**CR**
	Pr 4	ADC	55	Fem.	Never	del746-750	erlotinib	**CR**
	Pr 5	ADC	59	Fem.	Never	L858R	gefitinib	**CR**
	Pr 6	ADC	67	Fem.	Never	del746-750	erlotinib	PR
	Pr 7	ADC	53	Fem.	Never	L858R	erlotinib	PR
	Pr 8	ADC	67	Male	Never	L858R	erlotinib	PR
	Pr 9	ADC	64	Fem.	Never	L858R	erlotinib	PR
	Pr 10	ADC	55	Male	Never	L858R	erlotinib	primer: PR, meta:

Uncorrected Version. Published on February 8, 2008 as DOI:10.2353/jmoldx.2008.070125

Journal of Molecular Diagnostics, Vol. 10, No. 2, March 2008
Copyright © American Society for Investigative Pathology and the Association for Molecular Pathology
DOI:

Epidermal Growth Factor Receptor (EGFR) High Gene Copy Number and Activating Mutations in Lung Adenocarcinomas Are Not Consistently Accompanied by Positivity for EGFR Protein by Standard Immunohistochemistry

Ferenc Pinter,* Judit Papay,† Andrea Almasi,‡ Zoltan Sapi,† Edit Szabo,‡ Melinda Kanya,† Anna Tamesi,† Balazs Jori,* Edit Varkondi,‡ Judit Moldvay,§ Klara Szondy,§ Gyorgy Kari,‖¶ Massimo Dominici,‖ Pierfranco Conte,‖ Sandor Eckhardt,** Laszlo Kopper,† Richard Schwab,‖‖ and Istvan Petak*†‡

From KFI Medical Biotechnology and Healthcare Services,* Budapest, Hungary; the First Department of Pathology and Experimental Cancer Research† and the Department of Pulmonology,‡ Semmelweis University, Budapest, Hungary; Rational Drug Design Laboratories CRC,§ Budapest, Hungary; Pathobiochemistry Research Group,¶ Hungarian Academy of Sciences, Budapest, Hungary; National Institute of Oncology,**

case) to erlotinib or gefitinib, mutations were identified in eight cases, but IHC was negative in four of these tumors. These results indicate that molecular diagnostic methods appear to be most important for the identification of lung adenocarcinoma patients who may benefit from EGFR inhibitor treatments. (J Mol Diagn 2008, 10:000–000; DOI: 10.2353/jmoldx.2008.070125)

The detectable expression of the target protein of novel molecular targeted drugs is often assumed to both sufficient and necessary for predicting the efficacy of these novel drugs. The clinical experience with anti-epidermal growth factor receptor (EGFR) antibody therapy cetuximab in the treatment of colon carcinoma patients re-

VOLUME 23 · NUMBER 30 · OCTOBER 20 2005

JOURNAL OF CLINICAL ONCOLOGY | DIAGNOSIS IN ONCOLOGY

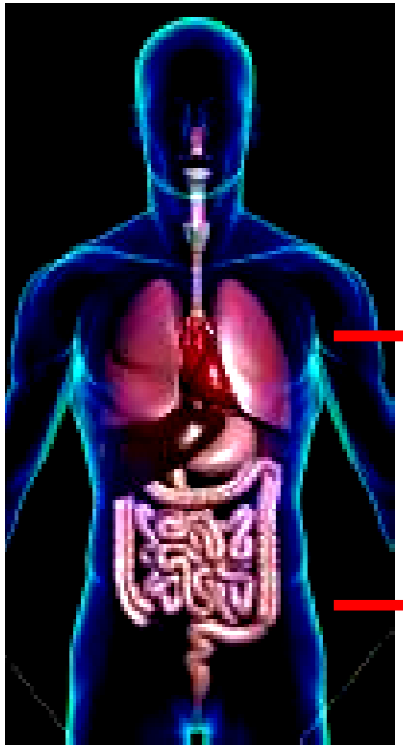
Modern Treatment of Lung Cancer

CASE 1. Amplification and Mutation of the Epidermal Growth Factor Receptor in Metastatic Lung Cancer With Remission From Gefitinib

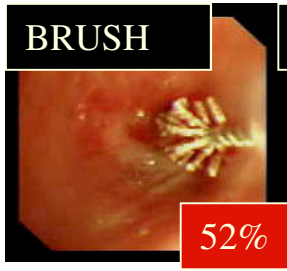
gestive of metastasis. She was continued on gefitinib, and in October 2004, she was found completely free of both brain and lung tumors.

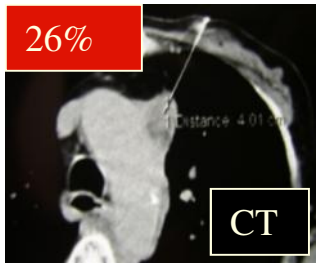
The epidermal growth factor receptor (EGFR) has been validated in several preclinical studies as an important tar-

SAMPLE TYPES FOR MOLECULAR PATHOLOGY



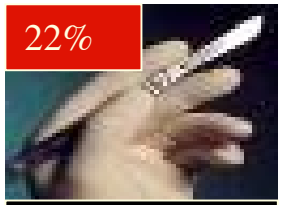
LUNG





CYTOLOGY SMEAR

EXCISOR

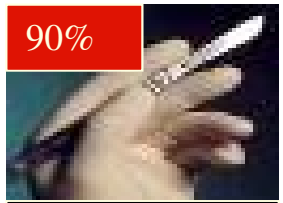


SURGICAL

FFPE BLOCK

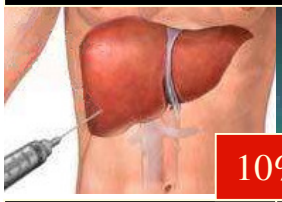
COLON

ENDSOCOPY

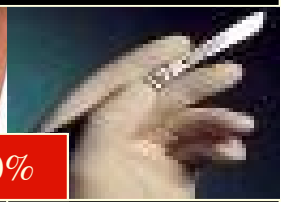


SURGICAL

LIVER METASTASIS

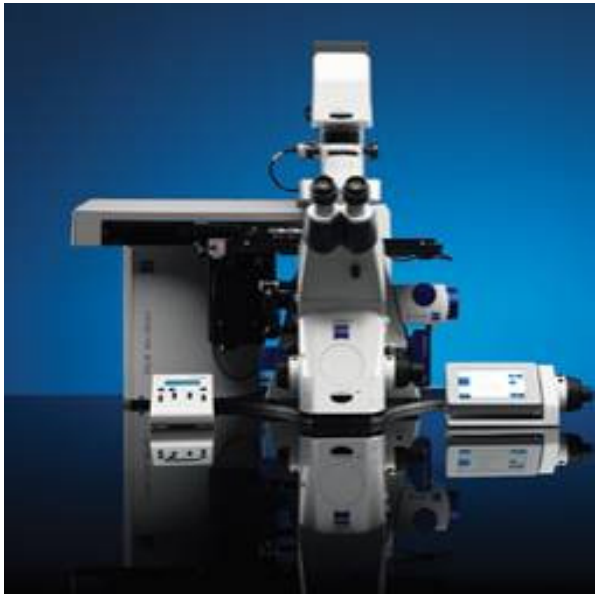


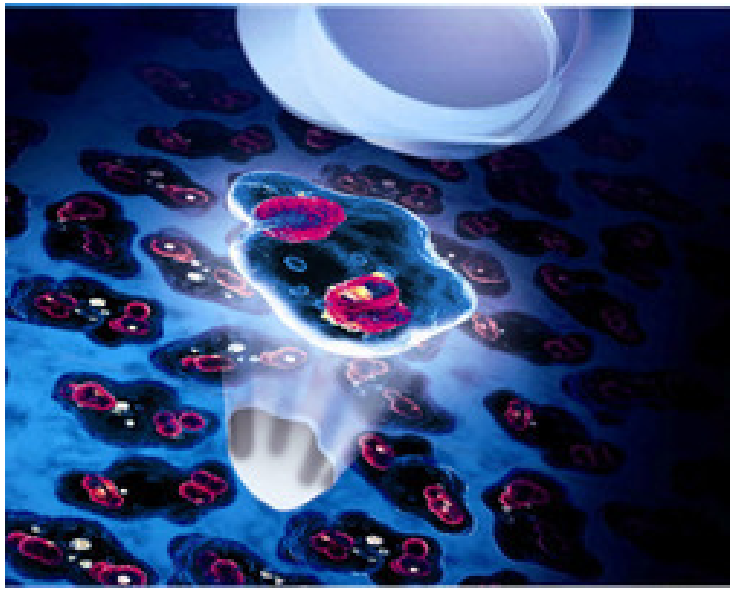
BIOPSY



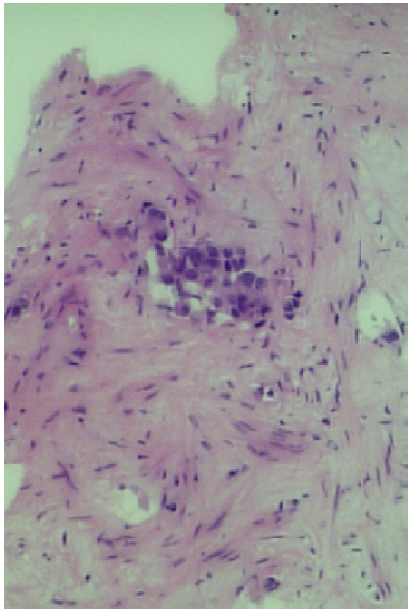
SURGICAL

SUCCESSFUL MULTIPLEX MOLECULAR PDX IN EXTREMELLY SMALL SAMPLES WITH ZEISS-PALM LASER CAPTURE MICROSCOPY BY TRANSFERING THE CELLS DIRECTLY FROM THE SLIDE TO THE PCR TUBE FOR AMPLIFICATION WITHOUT DNA EXTRACTION

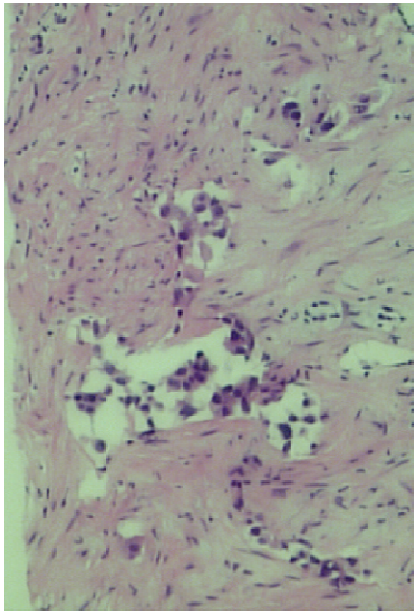




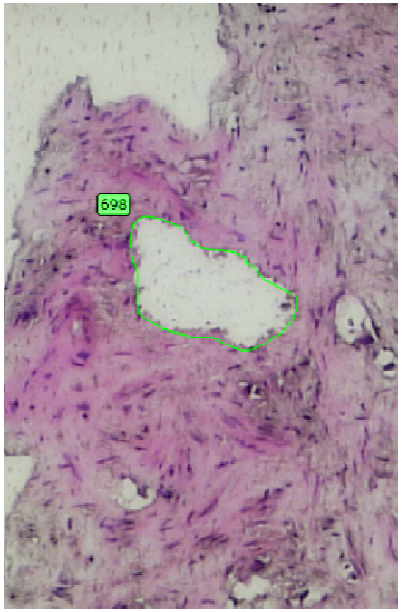
DETECTION OF EGFR MUTATION IN 84 CELLS

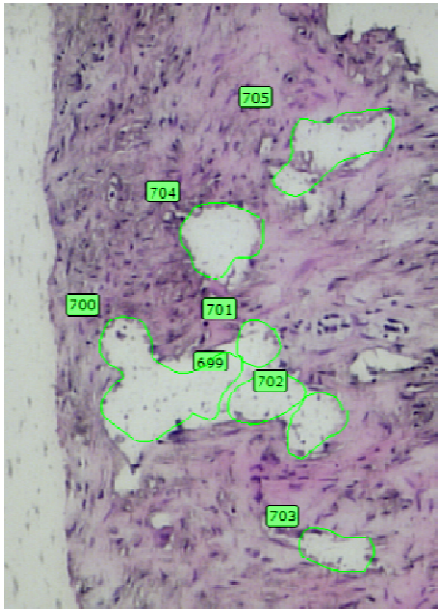


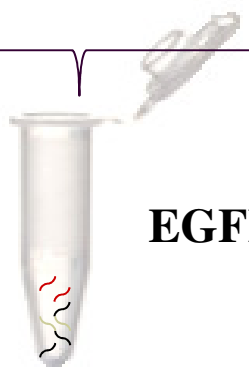
28 db



56 db



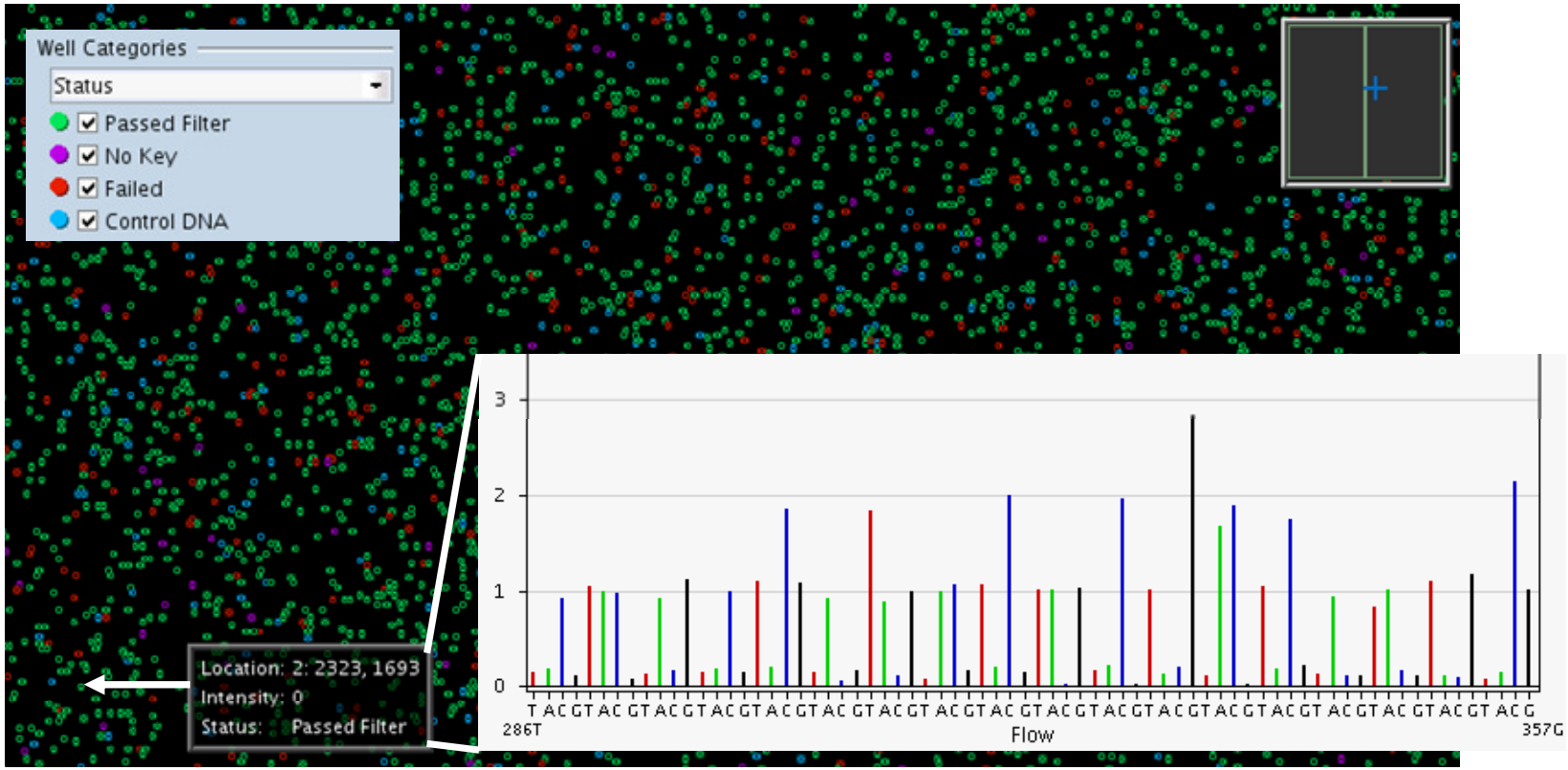




EGFR EXON 21
L858R

Response to gefitinib therapy

NEXT GENERATION CLONAL SEQUENCING CAN PROVIDE HIGH THROUGHPUT INFORMATION ON POTENTIAL TARGETS AND ALSO ABOUT THE MOLECULAR HETEROGENICITY



UP TO 1 MILLION PARALLEL PYROSEQUENCING
UP TO 1000 BP READ LENGTH

3X 100% RESULTS IN RING TRIALS

Molecular Diagnostic Laboratory
Department of Molecular Diagnostics
KPS Medical Biotechnology and Healthcare Services Ltd.
Budapest, Hungary

KRAS
European EQA program

European Society of Pathology

Score genotype: 10,0/10,0
Average score genotype (subscheme A): 9,9/10,0
Average score genotype: 9,4/10,0

Participated in the 2010 European KRAS External Quality Assessment Scheme

Dequeker E

Prof dr E Dequeker
Scheme co-ordinator

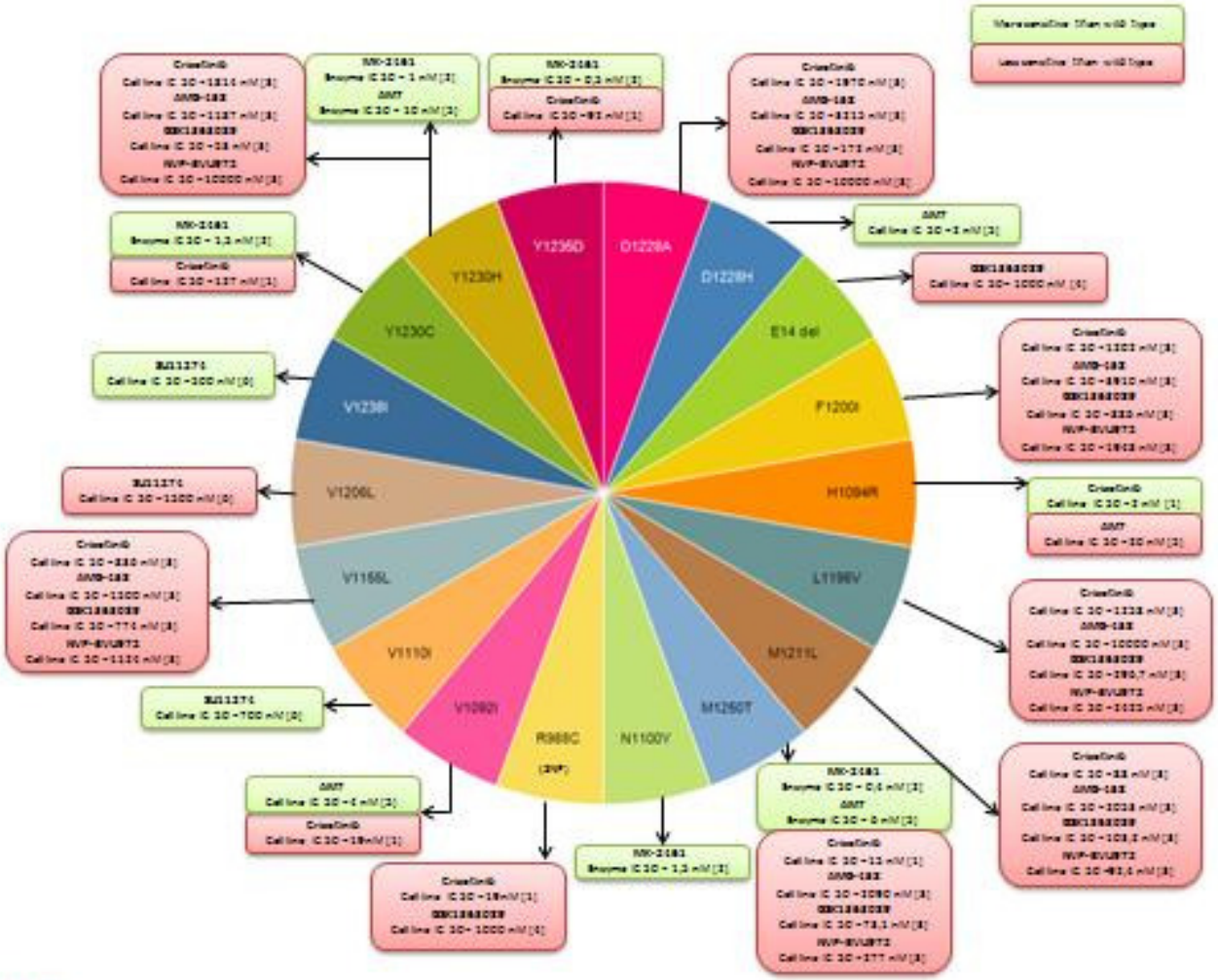
Prof dr J van Krieken
Medical / technical expert

ONCOMPASS TARGET

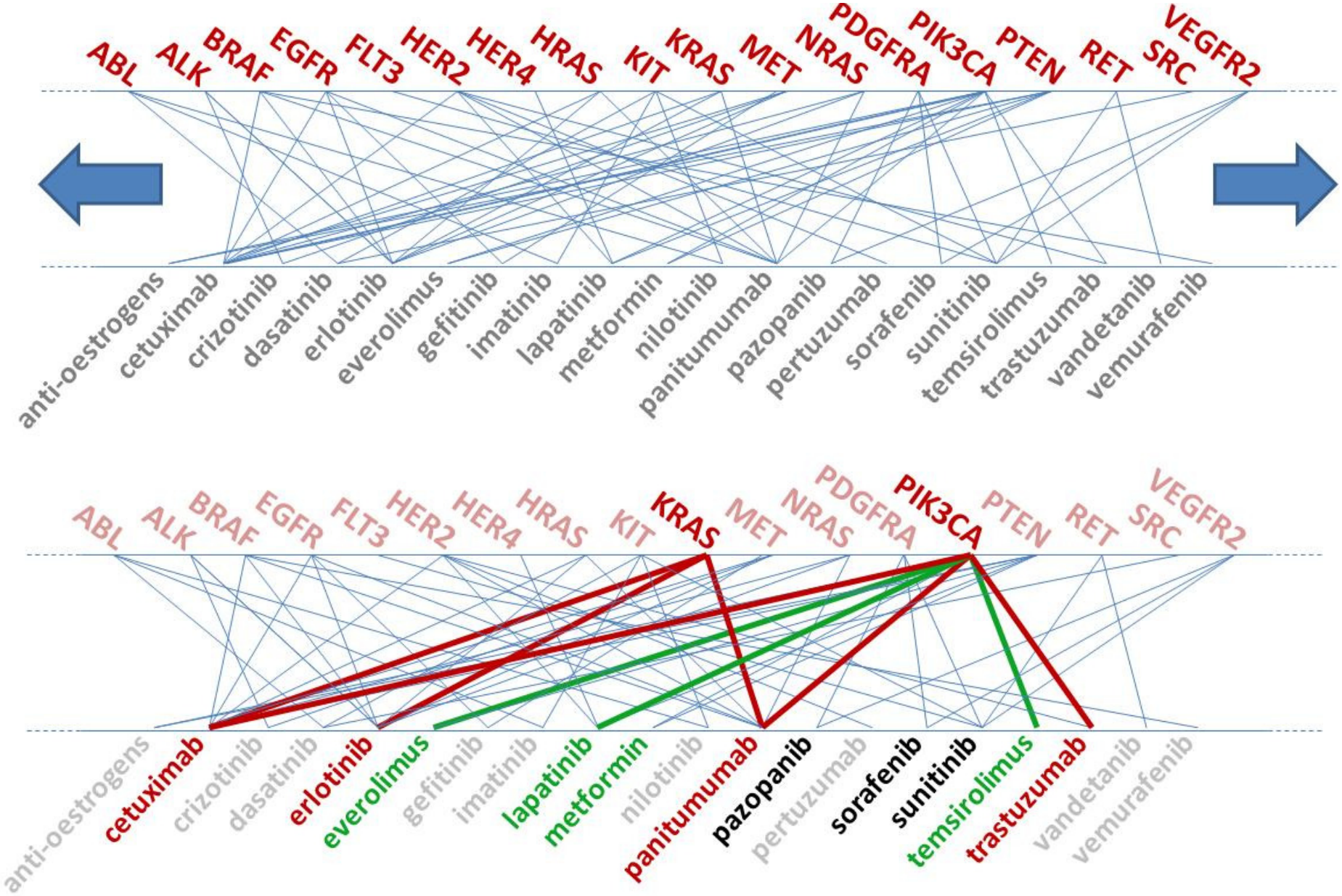
18 TARGETS	20 DRUGS
ALK:	crizotinib
BRAF	vemurafenib
EGFR:	erlotinib, gefitinib, cetuximab, panitumumab
ERBB2/HER-2	trastuzumab, lapatinib, pertuzumab,
ERBB4/HER-4	lapatinib
FLT3	sunitinib
KRAS	erlotinib, cetuximab, panitumumab
HRAS	cetuximab, panitumumab
NRAS	cetuximab, panitumumab
KDR (VEGFR2)	pazopanib, sunitinib, sorafenib
KIT	imatinib, sunitinib, dasatinib, nilotinib
PDGFR	sunitinib, pasopanib, sorafenib
RET	vandetanib, sunitinib
MET	crizotinib
ABL	imatinib, dasatinib, nilotinib
SRC	dasatinib
PIK3CA	everolimus,temsirolimus, metformin, cetuximab, anti-eostrogens
PTEN	everolimus, metformin cetuximab, anti-eostrogens

ONCOMPASS DRUG SENSITIVITY DATABASE

WT	Crizotinib	GSK1363089	NVP-BVU972	AM7	AMG-458	MK-2461	SU11274
Enzyme IC50 (nM)	4 [1]	0,4 [7]	14 [3]	17 [5]	8 [3]	2,5 [2]	10 [8]
Cell line IC50 (nM)	13 [1]	21 [7]	77 [3]	94 [5]	536 [3]	1000 [2]	1000 [9]

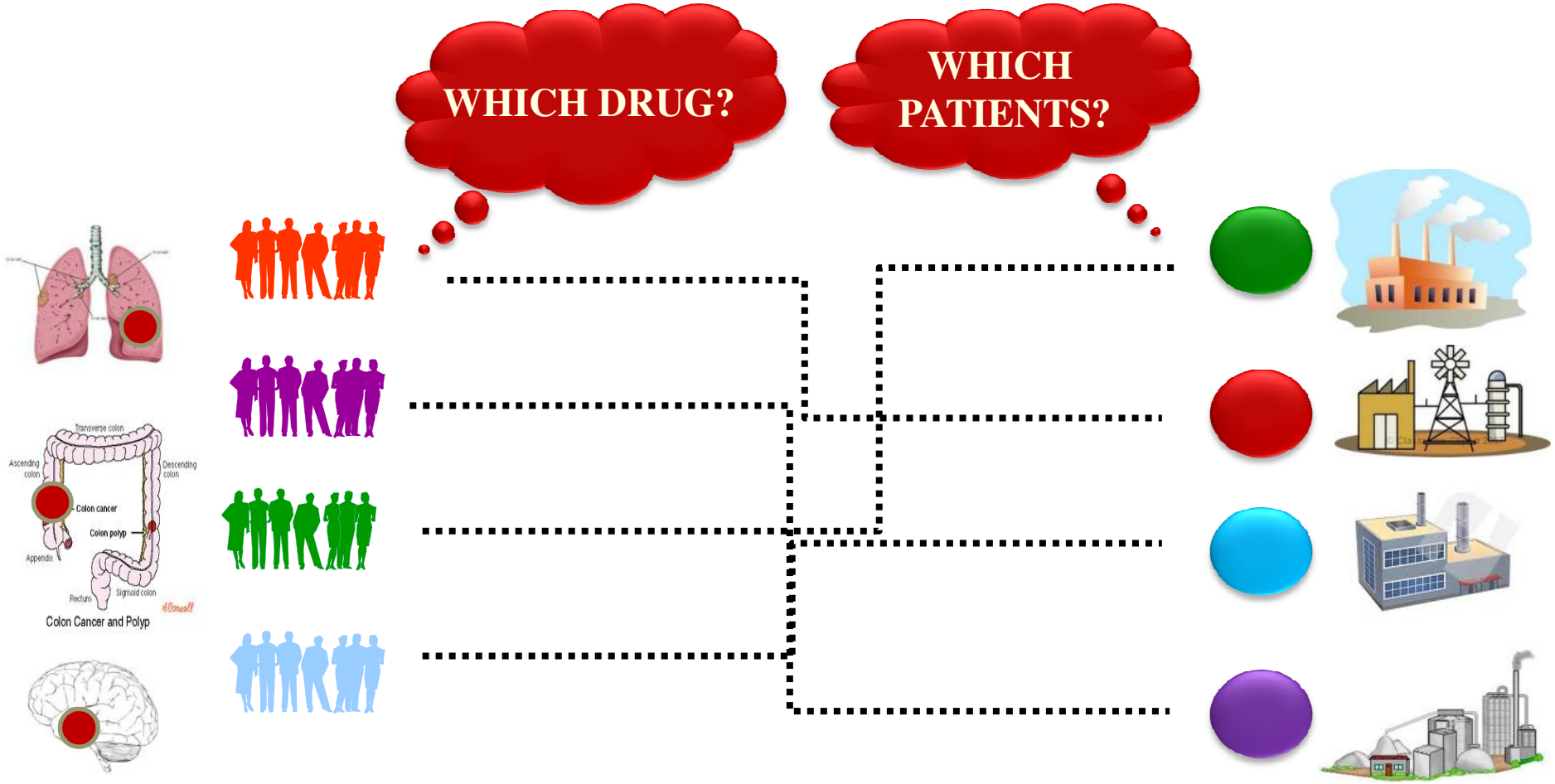


ONCOMPASS TARGET-DRUG ASSOCIATION ANALYZER

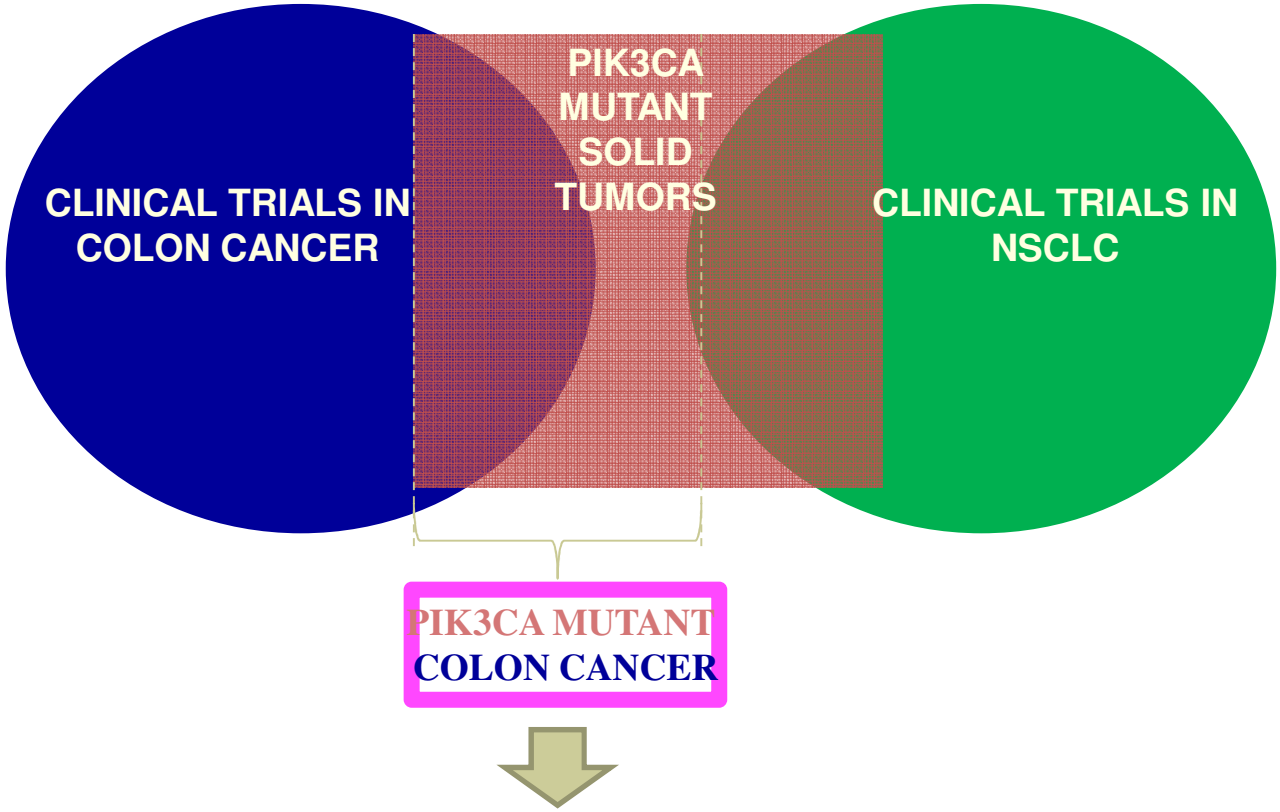


~100 TARGETS

~400 DRUGS

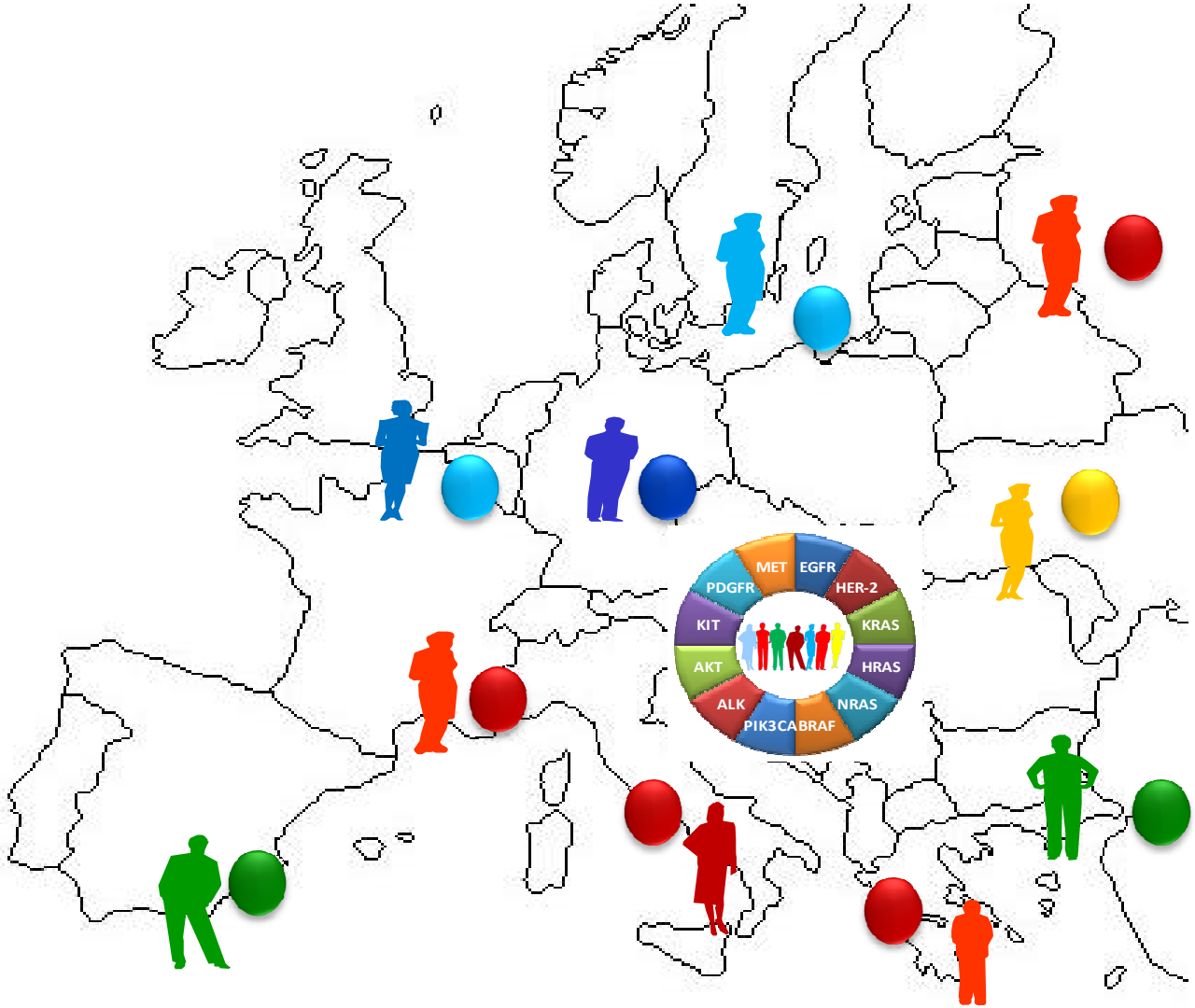


ONCOMPASS TARGETED CLINICAL TRIAL DATABASE



BIOMARKER	PIK3CA INHIBITORS	ORGAN	LINE	TYPE	OTHER MARKER	.....
PIK3CA	BKM120	COLON	2nd	Phase 1,II	KRAS WT	.....
PIK3CA	BYL719	SOLID TUMORS	2nd	Phase I.	PIK3CA M+/AMP	.....
PIK3CA	temsirolimus	SOLID TUMORS	-	Phase I	PIK3CA/ PTEN M+	.....
.....	.....	.....	.....	.....	.....	.....

ONCOMPASS
TARGETED CLINICAL TRIAL NAVIGATOR AND PATIENT ASSISTANCE



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