Translation of (cancer) genomes

Ultan McDermott

Cancer Genome Project

"Decoding the genome has led to stunning advances in scientific knowledge and DNA-processing technologies but it has relatively little to improve medical treatments or human health." (New York Times, June 20, 2010)

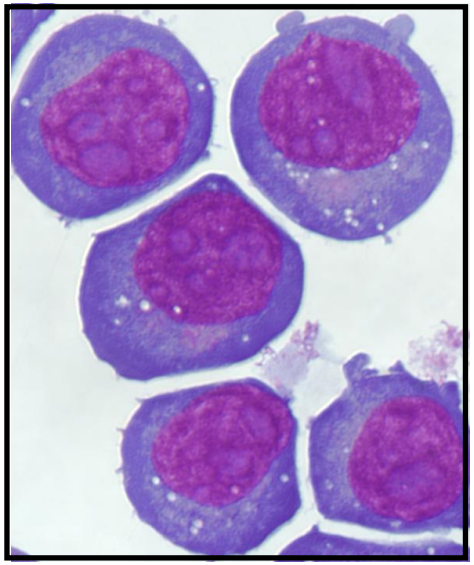
"The subtlety of Nature far surpasseth the subtlety of Man's understanding." (Francis Bacon; 1561-1626)

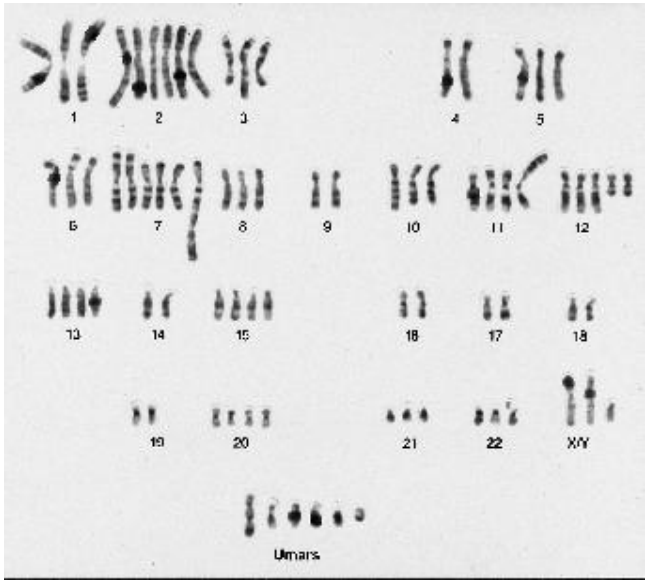
Background

- During a lifespan, 41% of the US population will develop cancer and 21% will die from cancer
- Biggest improvements in survival – early detection, prevention strategies, better surgery
- Cancer is a genomic disease
- Can next-gen sequencing improve survival by offering more effective treatments?

Cancer

A Disease of the Genome



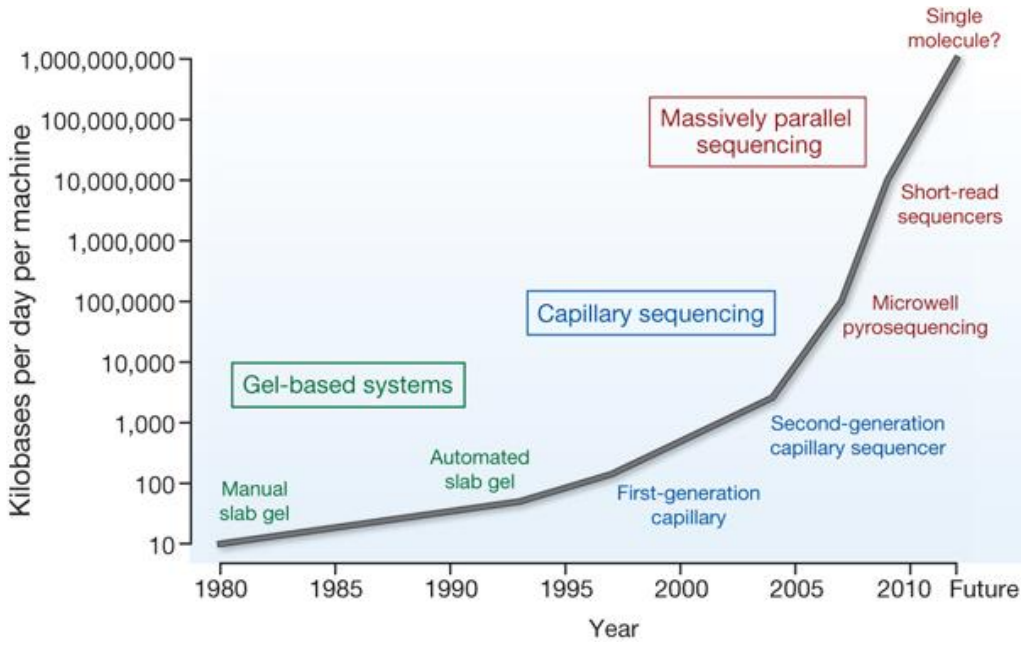


Challenge in Treating Cancer:

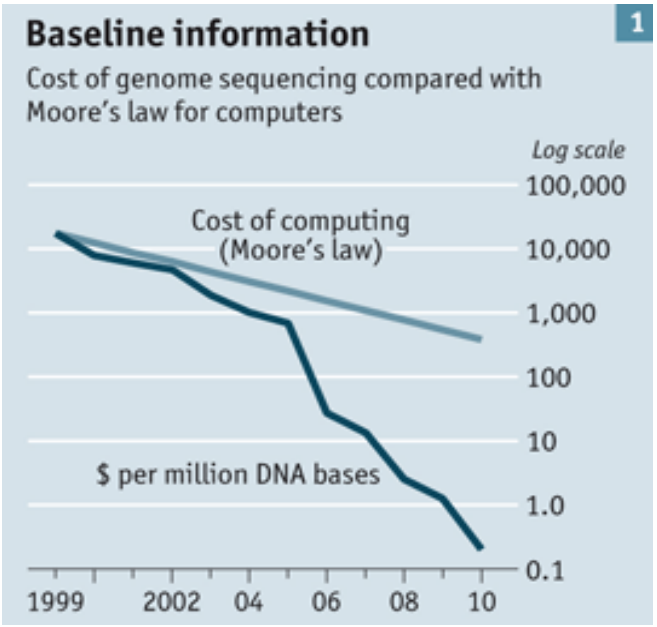
- Every tumor is different
- Every cancer patient is different

Improvements in the rate of DNA sequencing

Increased data....

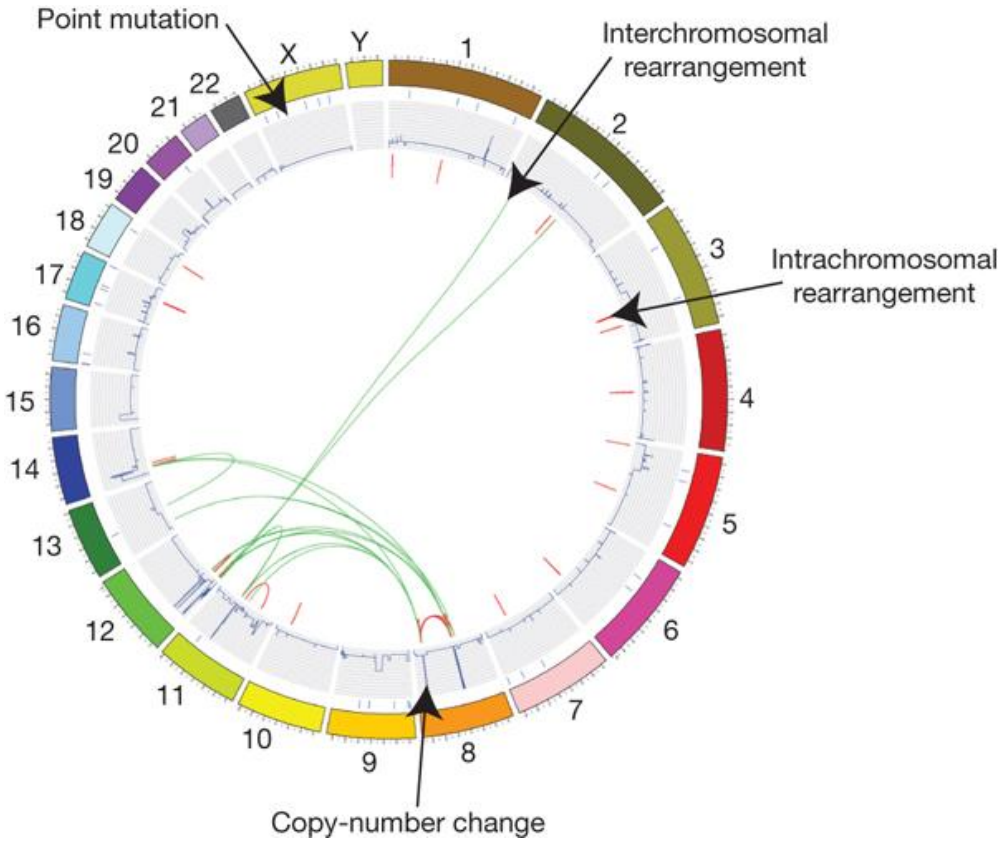


...decreased cost

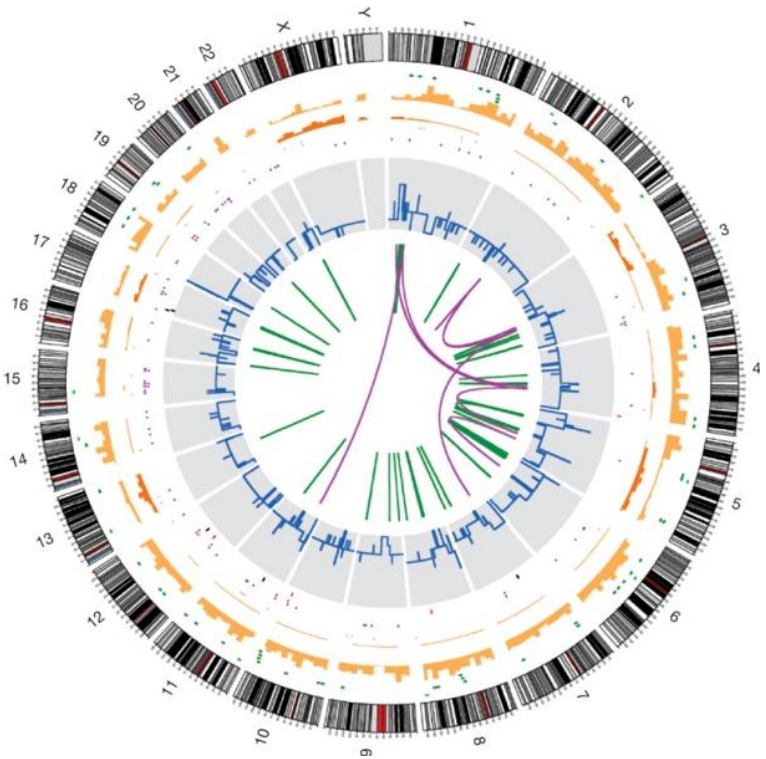


Catalogue of somatic mutations in cancer cell lines

NCI-H2171



NCI-H209



MR Stratton *et al. Nature* **458**, 719-724 (2009)

ED Pleasance *et al. Nature* **000**, 1-7 (2009)

EDITORIAL

The Genome, 10 Years Later

Published: June 20, 2010

On June 26, 2000, two scientific teams announced at the White House that they had deciphered virtually the entire human genome, a prodigious feat that involved determining the exact sequence of chemical units in human genetic material. An enthusiastic President Clinton predicted a revolution in "the diagnosis, prevention and treatment of most, if not all, human diseases."

Now, 10 years later, a sobering realization has set in. Decoding the genome has led to stunning advances in scientific knowledge and DNA-processing technologies but it has done relatively little to improve medical treatments or human health.

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THE TIMES
THE SUNDAY TIMES

Archive Article Please enjoy this article from The Times & The Sunday Times archives. For full

From The Sunday Times

June 13, 2010

Genetics to solve why Ozzy Osbourne is still alive

Jack Grimston

THE mystery of why Ozzy Osbourne is still alive after decades of drug and alcohol abuse may finally be solved.

The 61-year-old former Black Sabbath lead singer — who this week begins his health advice column in The Sunday Times Magazine — is to become one of only a few people in the world to have his full genome sequenced.

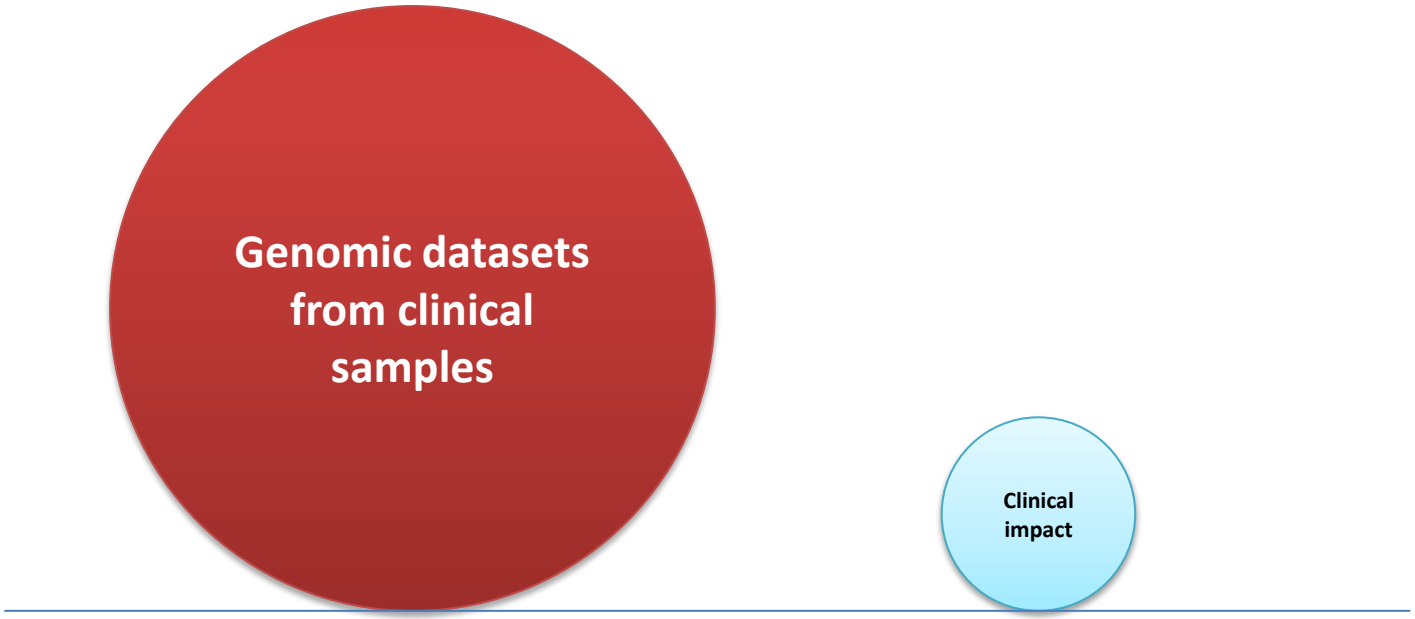
In addition to giving Osbourne information that could help prevent diseases, it is hoped the results will provide insights into the way drugs are absorbed into the body.

The first full genome was sequenced in 2003 after 13 years of work. Today, analysing a genome takes three months and costs about £27,000.

EXPLORE HEALTH NEWS

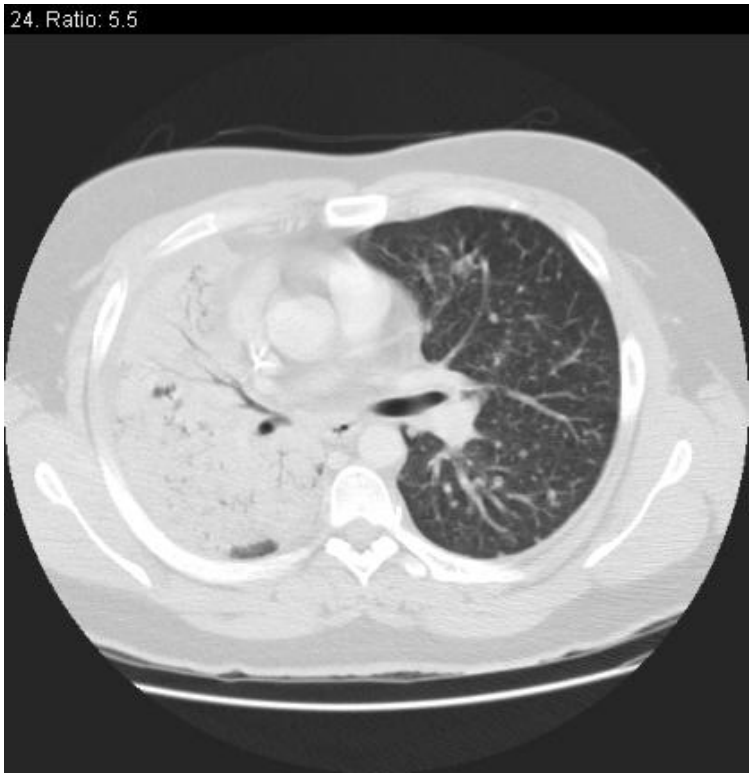
› SWINE FLU

The elephant in the room...

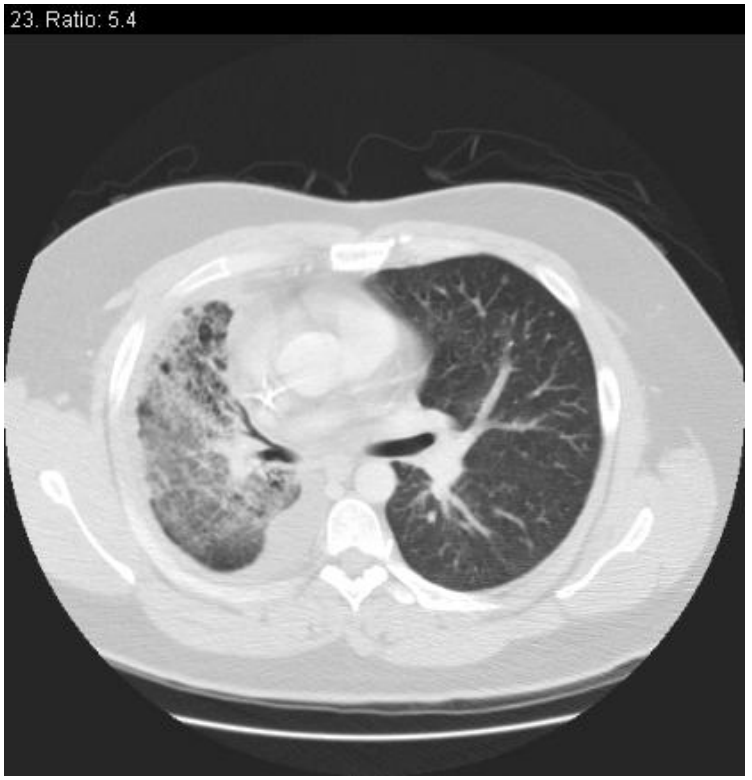


Rapid & dramatic response to gefitinib in a NSCLC patient

Before Gefitinib



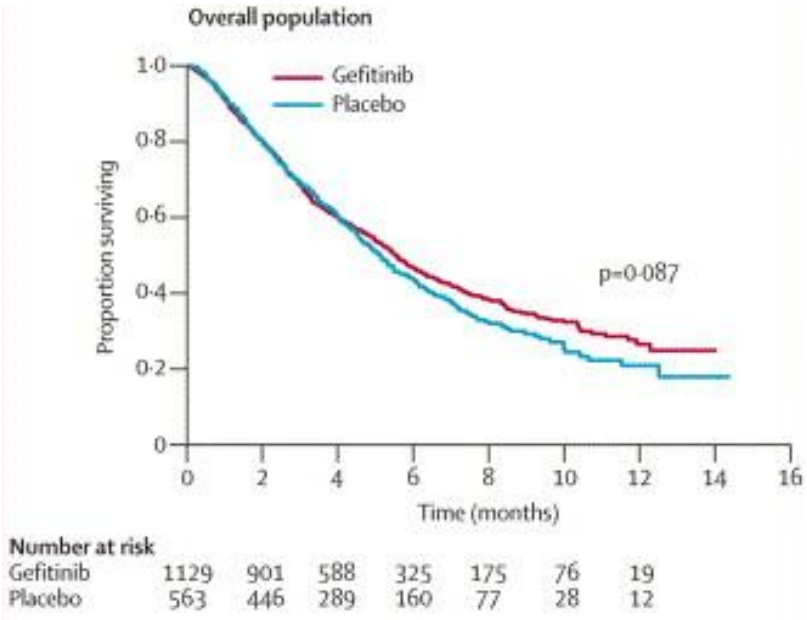
After Gefitinib (6 weeks)



But responses are limited to 10-20% of treated patients = EGFR mutations

Traditional trial design versus targeted

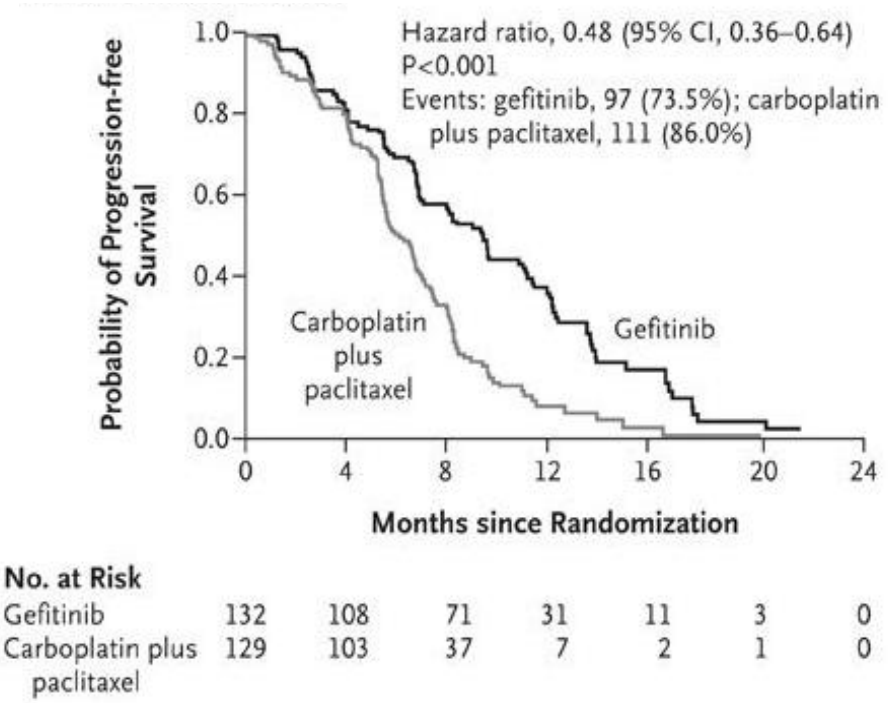
ISEL study (2005)
Gefitinib vs placebo in NSCLC



EGFR mutation: RR 38%
EGFR wild-type: RR 3%
Cost: $44 million

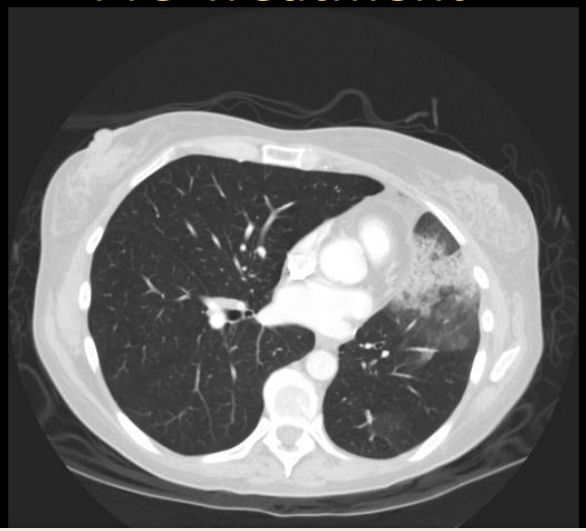
Mok et al (2009)
Gefitinib vs 1st line chemo

EGFR-Mutation-Positive

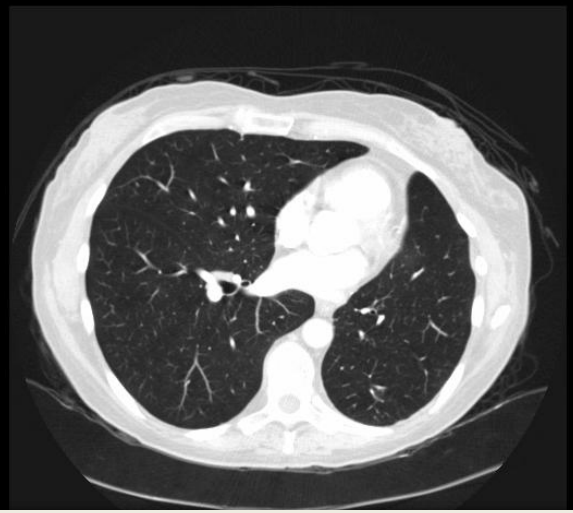


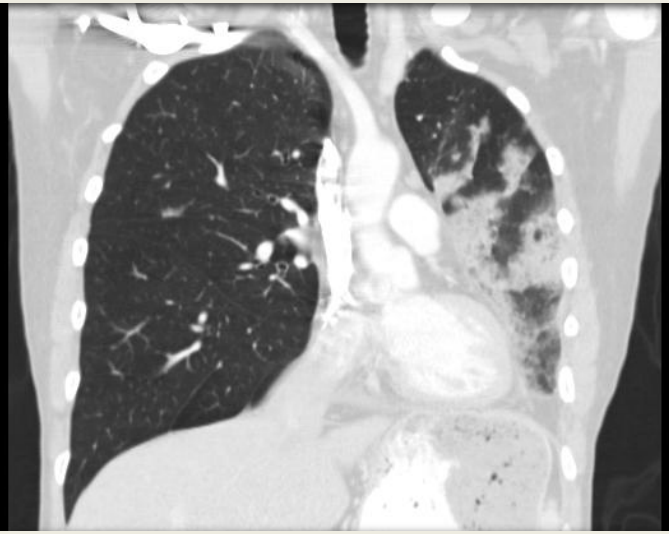
46 yr old Male Non-Smoker with NSCLC ALK Fusion

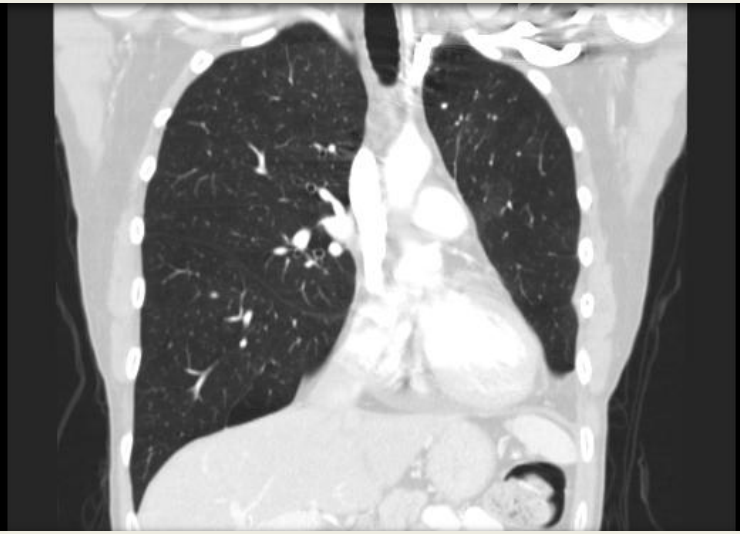
Pre-Treatment



After 2 Cycles PF-2341066

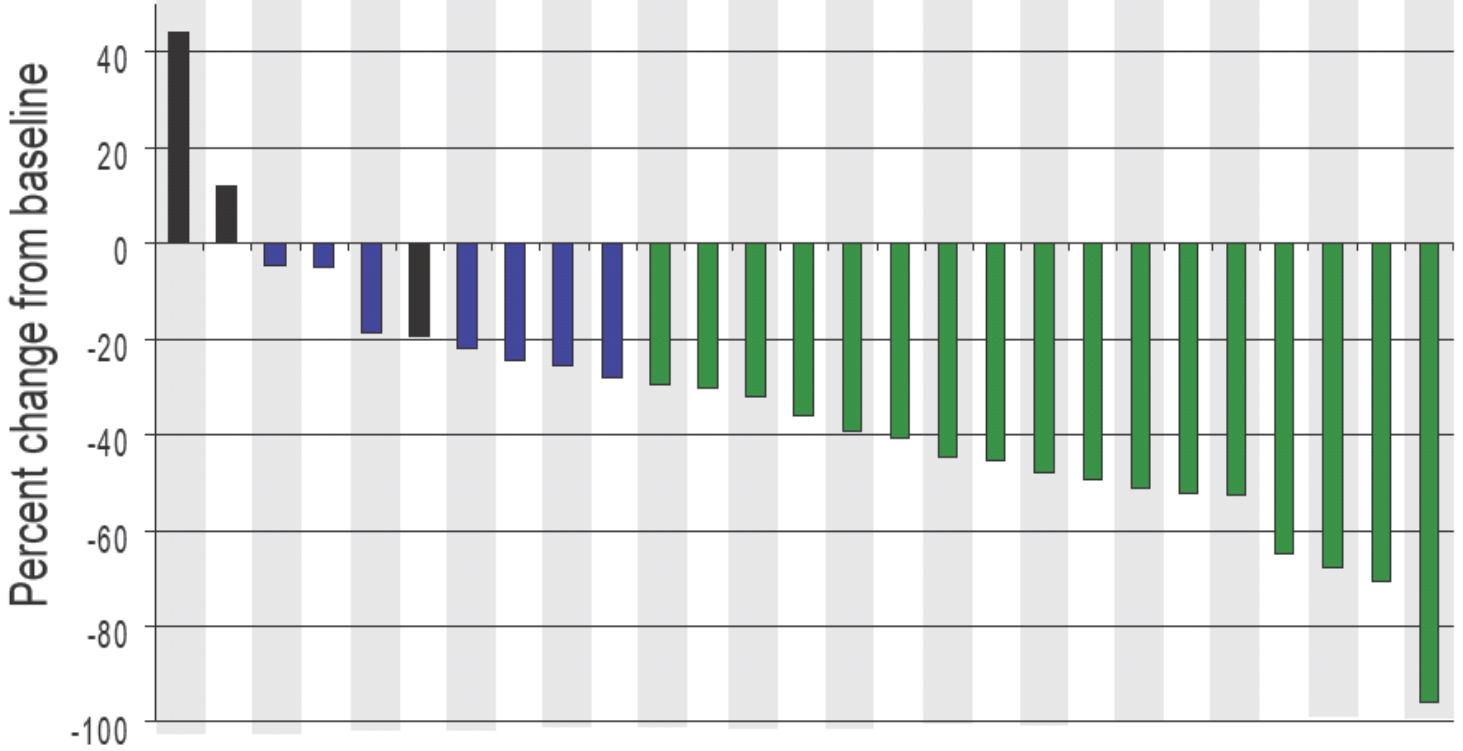






Tumour Responses to PF-2341066 for NSCLC

Subject	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
% Response	40	16	4.4	5	18.7		22	24	26	28	30	30	32	36	40	41	45	45	48	50	51	52	53	65	68	71	96
Treatment Duration			38	14+	15+		14	31+	9	24+	15+	20	16+	11+	10+	19	30	17+	21+	16+	8+	41+	11+	26	41+	46+	19+
EML4 ALK Genotype	---	6	13	13	13	---	Neg	Neg	18	---	---	---	---	13	13	20	6	Neg	13	13	13	13	13	---	6b	13	---
ALK expression	---	2+	1+	1+	---	---	2+	2+	2+	---	2+	1+	---	2+	1+	3+	2+	1+	2+	2+	3+	2+	---	---	3+	2+	---

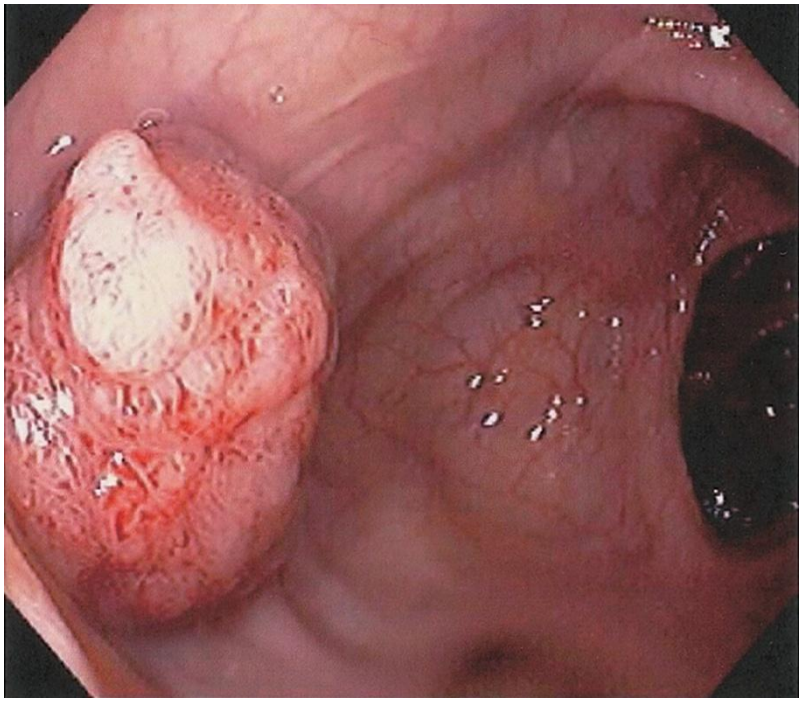


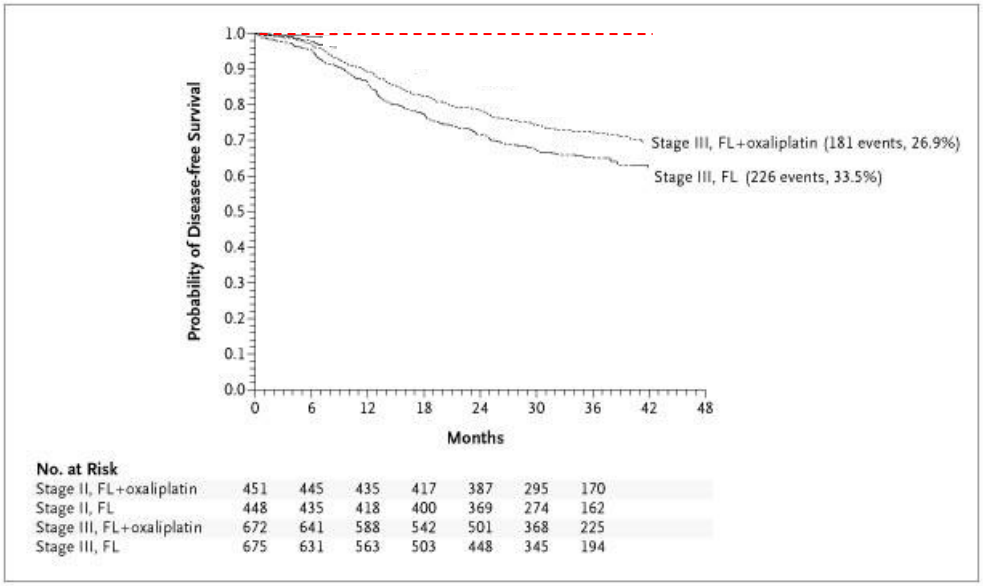
Targeted therapies in cancer

Kinase	Alteration	Tumour types	Therapeutic agent
Receptor tyrosine kinases			
EGFR	Mutation, amplification	Lung, GBM	Gefitinib, erlotinib
ERBB2	Amplification	Breast	Lapatinib
FGFR1	Translocation	CML	PKC412, BIBF 1120
FGFR2	Amplification, mutation	Gastric, breast, endometrial	PKC412, BIBF 1120
FGFR3	Translocation, mutation	Multiple myeloma	PKC412, BIBF 1120
PDGFR alpha	Mutation	GBM, GIST	Sunitinib, sorafenib, imatinib
PDGFRA beta	Translocation	CMML	Sunitinib, sorafenib, imatinib
ALK	Mutation/amplification	Lung, neuroblastoma, ALCL	PF-2341066
c-MET	Amplification	Gefitinib-resistant NSCLC, gastric	PF-2341066, XL184, SU11274
IGF-1R	Activation by IGF-II ligand	Colorectal, pancreatic	CP 751 871, AMG479
c-KIT	Mutation	GIST	Sunitinib, imatinib
FLT3	Internal tandem duplication	AML	Lestaurtinib, XL999
RET	Mutation, translocation	Thyroid medullary carcinoma	XL184
Non-receptor tyrosine kinases			
Abl	Translocation (Bcr-Abl)	CML	Imatinib
JAK2	Mutation (V617F), translocation	CML, MPD	Lestaurtinib, INCB018424
Serine/threonine/lipid kinases			
BRAF	Mutation (V600E)	Melanoma, colon	SB-590885, PLX-4720, RAF265, XL281
PI3K	PIK3CA mutations	Colorectal, breast, GBM, gastric	BEZ235

Patient JS; 56-year old architect

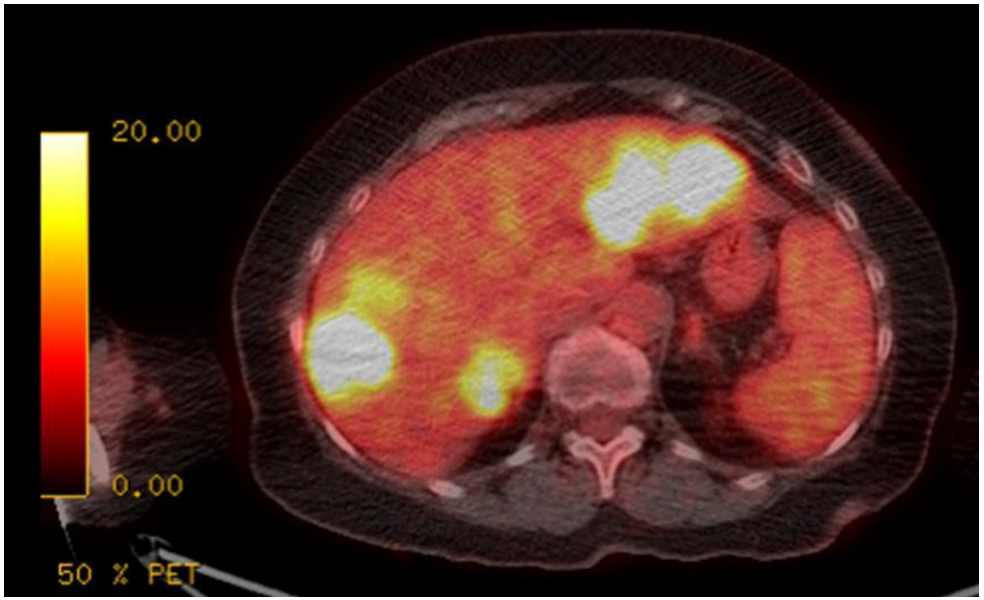
6 month history of altered bowel habit, weight loss, bleeding

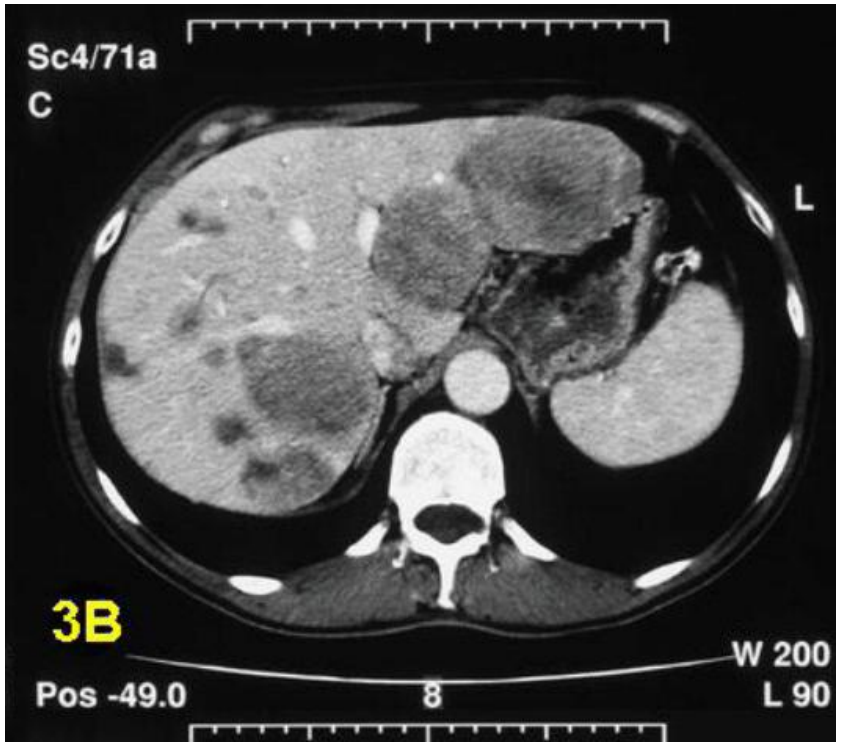




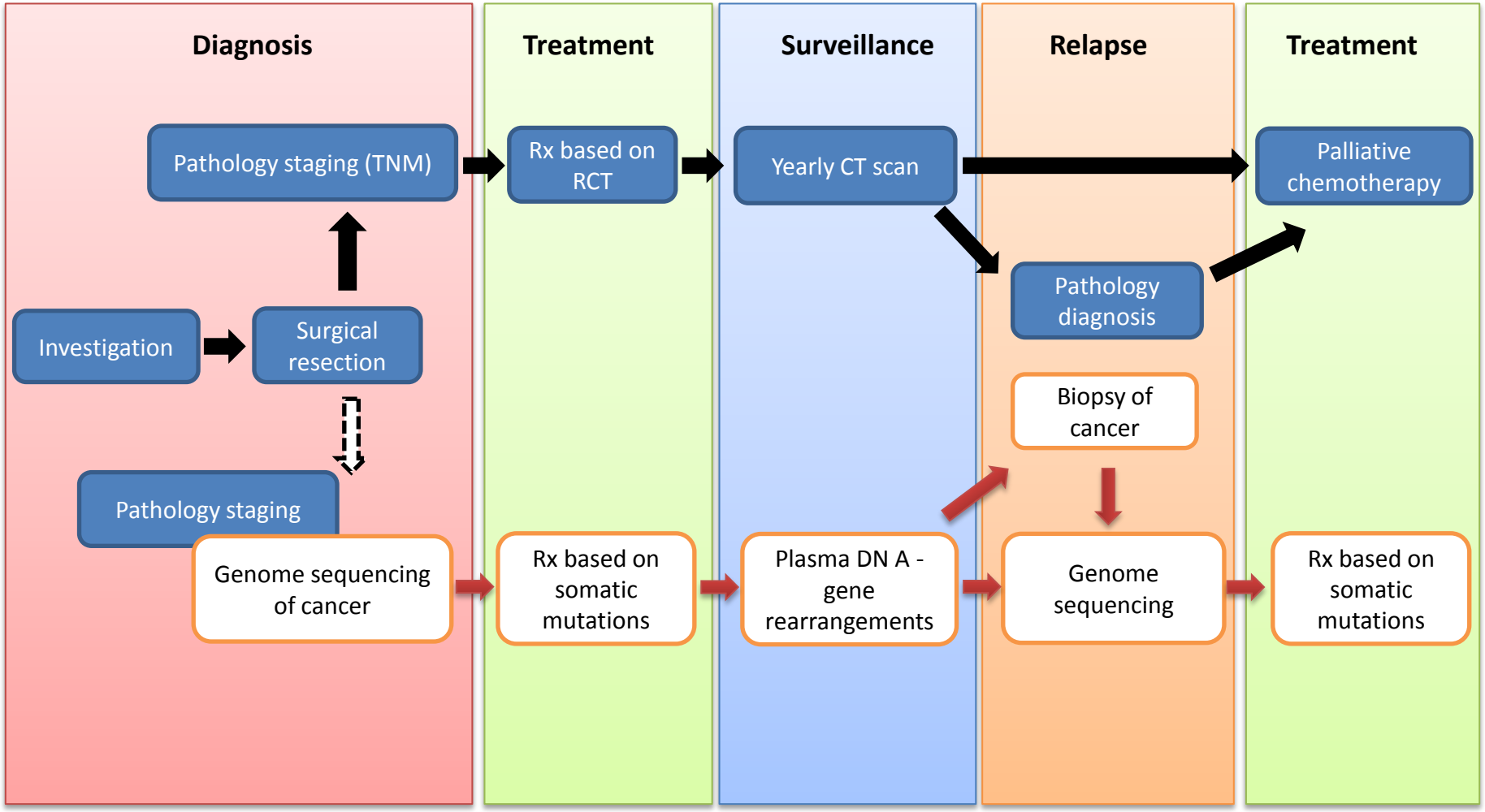
Patient JS

2 years later – right-sided abdominal pain, nausea, weight loss

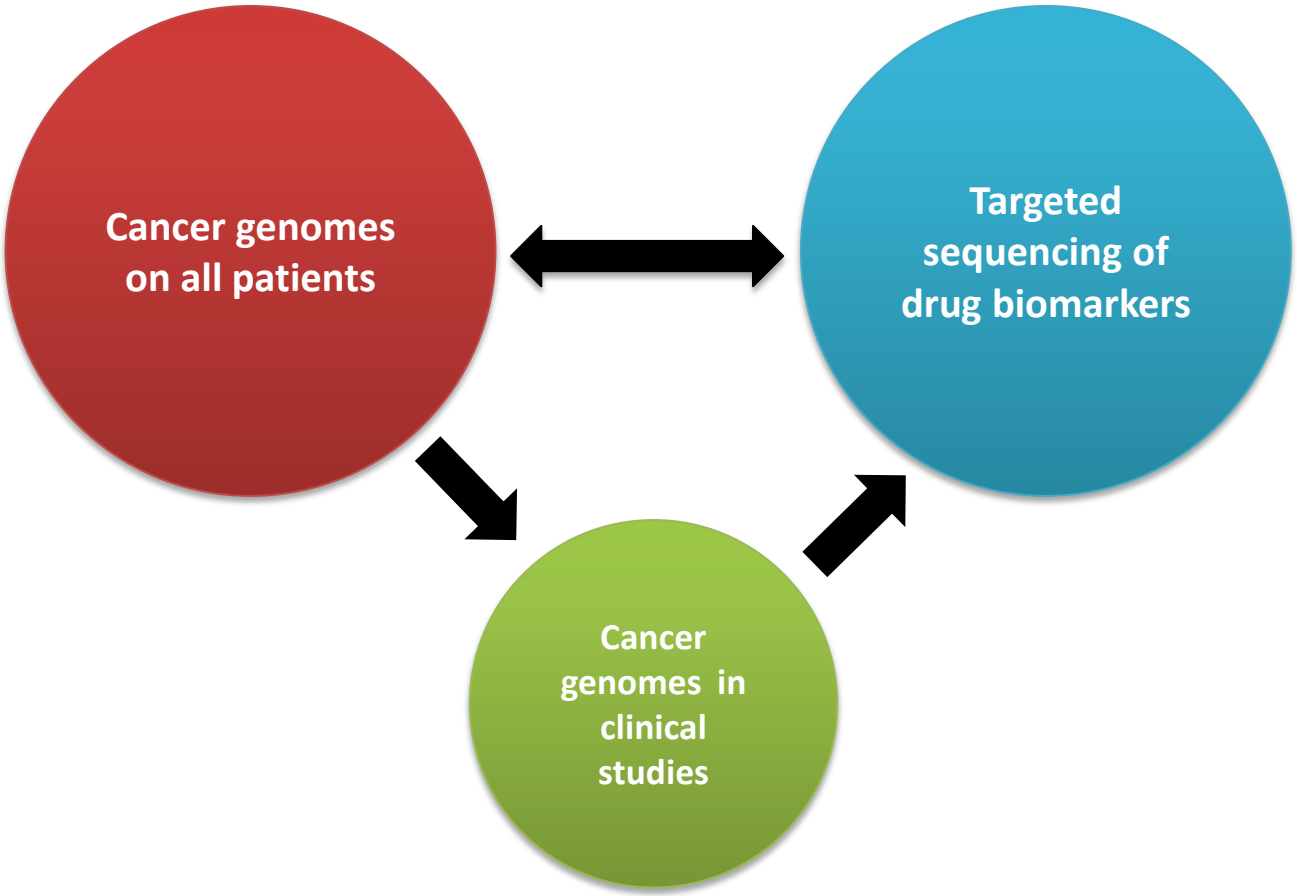




Current NHS cancer management



The future of genomics in the NHS



And the winners are...

- Expertise in next-gen sequencing (clinical samples) ✔
- In vitro model organisms to define biologically significant mutations ✔
- High-throughput screens of the latest cancer drugs from pharma ✔
- Bioinformatics expertise to identify driver genes ✔
- Strategic alliances with industry ✔
- International leadership ✔