

Personalized (Cancer) Medicine

PM16 – Precision Medicine Course
Day 1 – September 27th 2016

Outline

1. Cancer Genomics

2. Personalized Medicine

3. Bioinformatics Methodologies

4. CNIO personalized Medicine initiative

INTRODUCTION

The Path to Genomic Medicine

Human Genome first draft



Genomic
Medicine



Human
Genomic
Variation



1000 Genomes
A Deep Catalog of Human Genetic Variation

Genomic Basis of
Human Diseases
GWAS



Function of the
Human Genome
Sequence



Routine Whole-
Genome
Sequencing



Routine Analysis
of Genome
Sequences



New Diagnosis?
New Treatments?



Molecular Biology
Revolution

Genome Sequencing
Revolution

Analysis Revolution

Medicine Revolution

10 years ago

TODAY

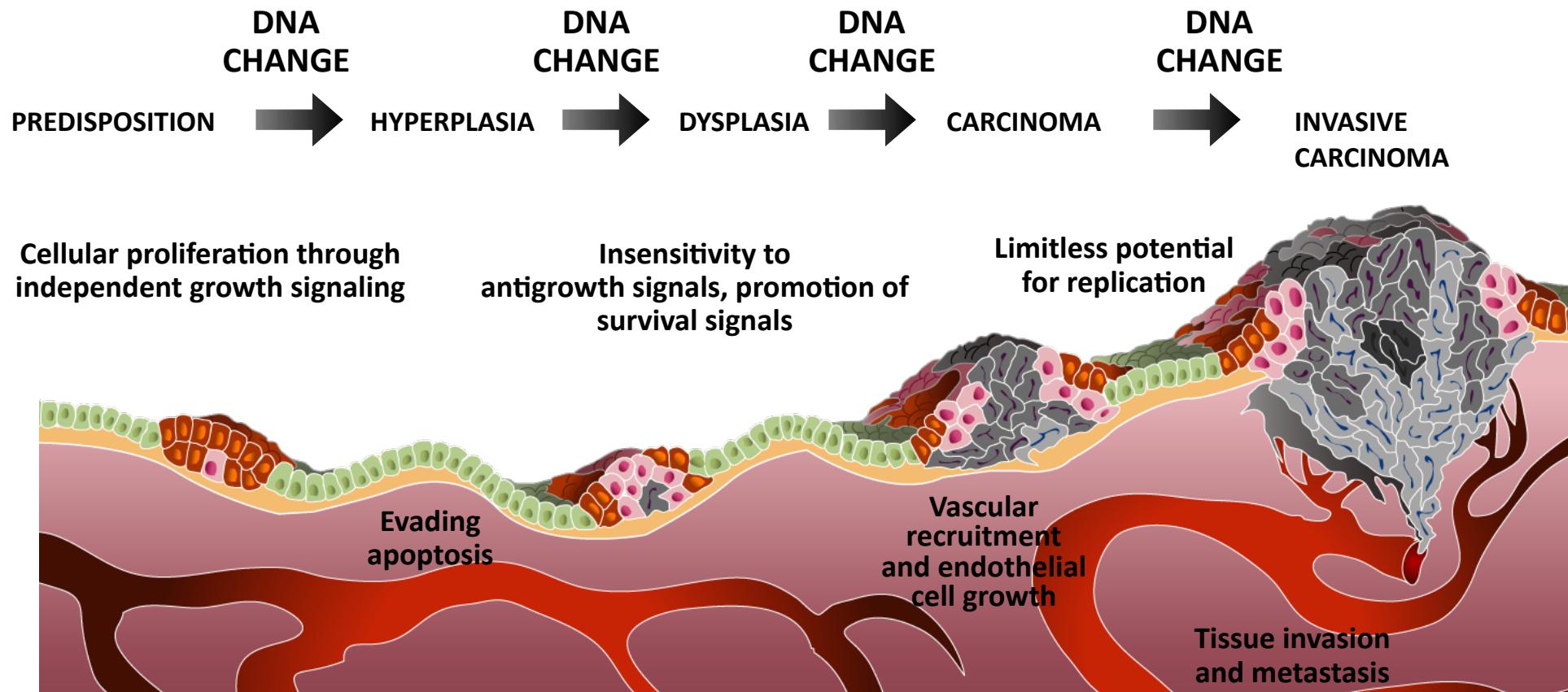
The future



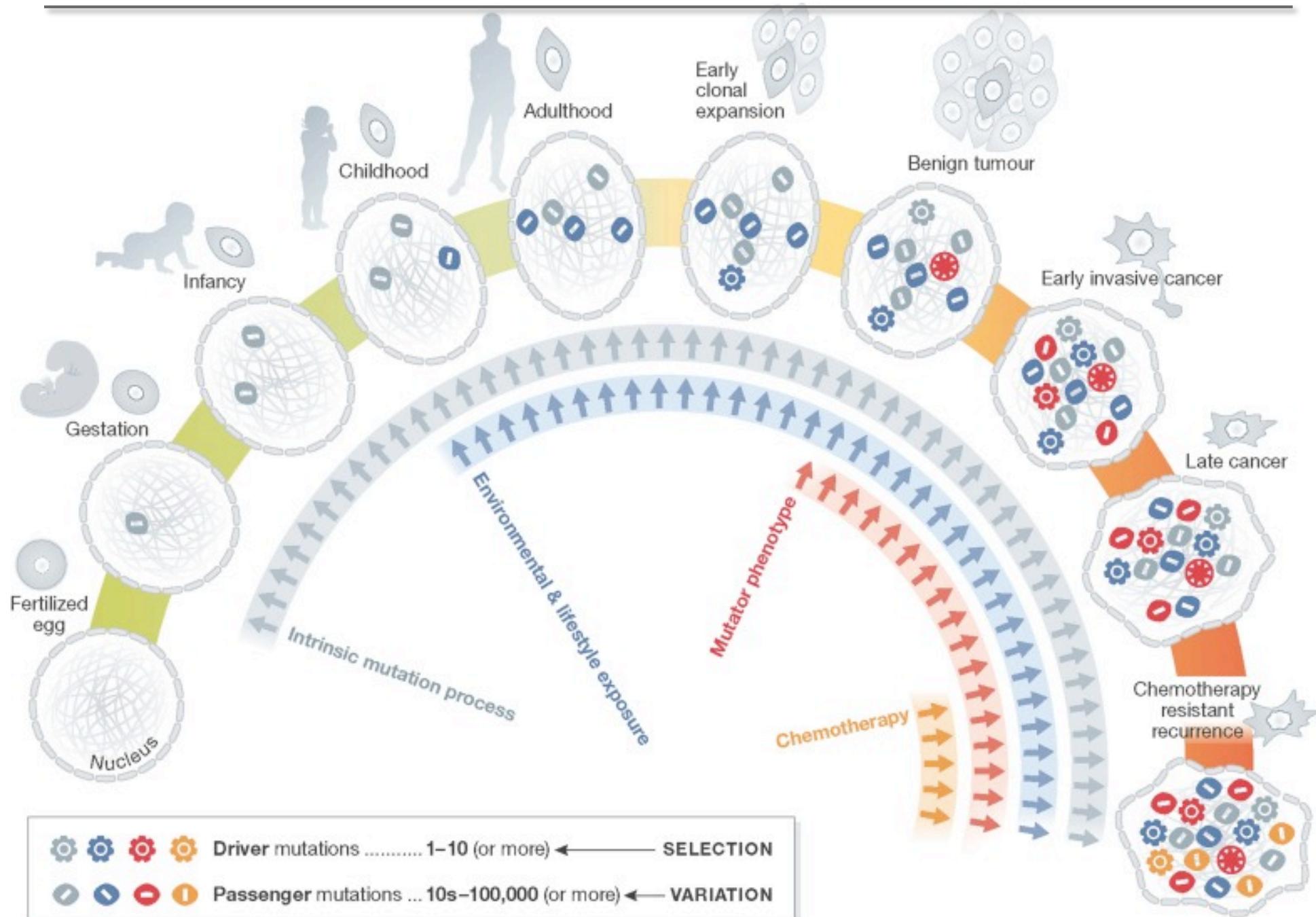


CANCER IS A GENETIC DISEASE

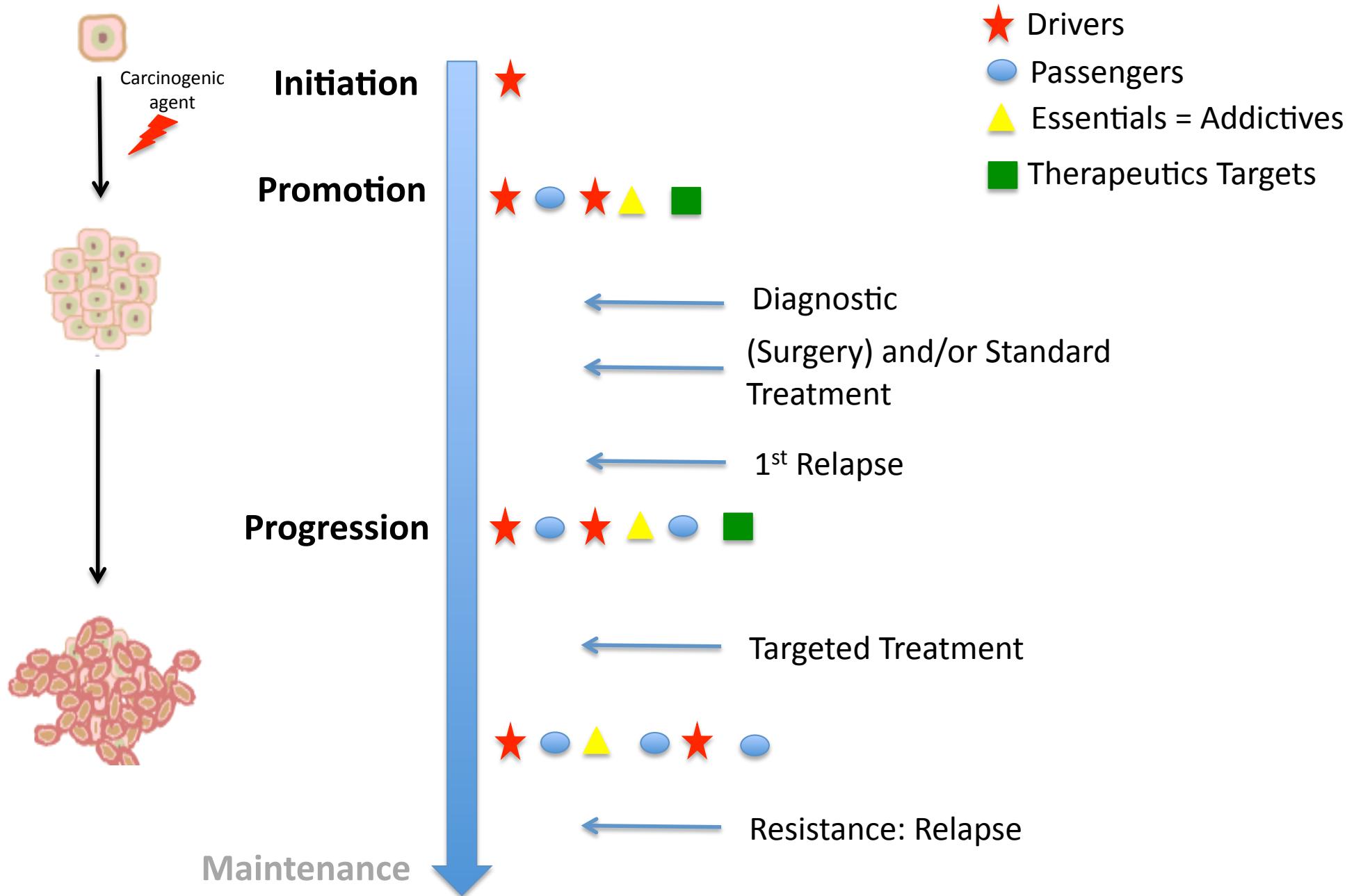
Cancer arises through a series of somatic alterations in DNA that result in unrestrained cellular proliferation. Most of these alterations involve actual sequence changes in DNA (i.e., mutations). They may originate as a consequence of random replication errors, exposure to carcinogens (e.g., radiation), or faulty DNA repair processes. While most cancers arise sporadically, familial clustering of cancers occurs in certain families that carry a germline mutation in a cancer gene.

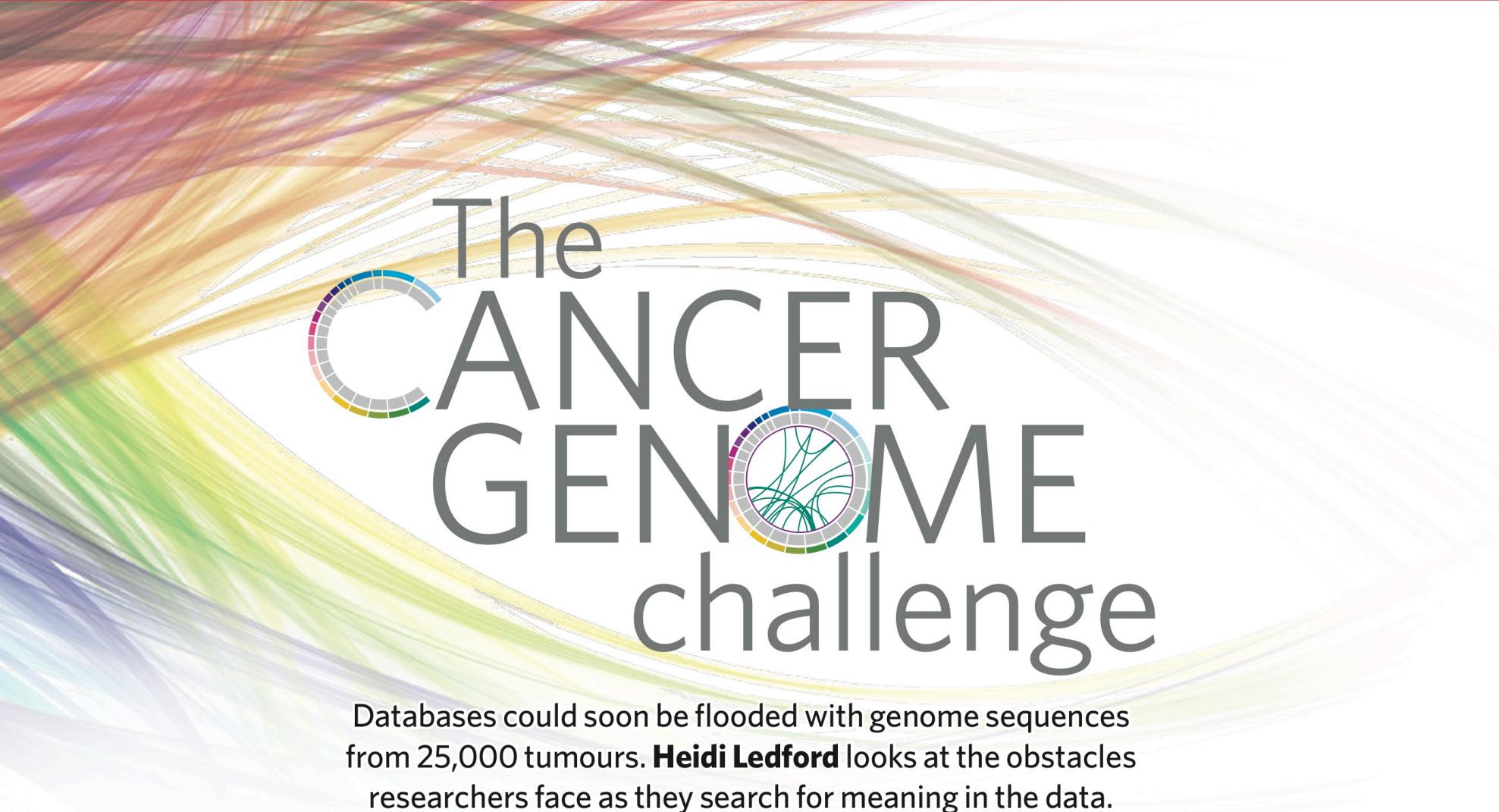


Tumor cell development



Carcinogenesis





The CANCER GENOME challenge

Databases could soon be flooded with genome sequences from 25,000 tumours. **Heidi Ledford** looks at the obstacles researchers face as they search for meaning in the data.

Cancer Genomics Goals



- **Establishing a Reference Cancer Genome (Structural)**
 - Known all driver genes in all types of cancer
 - Know how all driver genes correlate with clinical phenotype

- **Cancer Therapeutic Roadmap (Functional)**
 - Recognize functional pathways in which targets function
 - Know cancer vulnerabilities, as function of cancer genome (targets)
 - Know resistance mechanisms, as function of cancer genome (combinations)

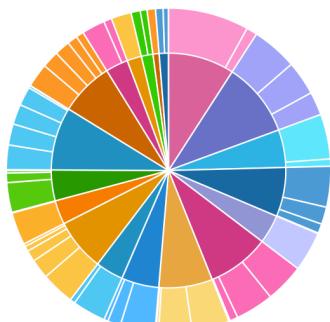


Cancer genomics data

Bioinformatics will be far more than genome sequence data



International
Cancer Genome
Consortium

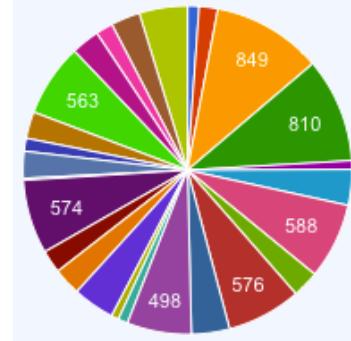


ICGC: 55 Cancer projects
12,979 samples



NATIONAL
CANCER
INSTITUTE
genome.gov
National Human Genome Research Institute
National Institutes of Health

The CANCER GENOME ATLAS



TCGA: 43 Cancer projects
13,106 samples



COSMIC Genomes
Catalogue of somatic mutations in cancer

COSMIC Whole Genomes

Cancer gene discovery studies are increasingly utilising whole-genome sequencing technologies, generating a range of coding and non-coding mutation annotations and revealing substantially more detail about the genetic state of each tumour... [\[More\]](#)

Statistics

Genes	22170	Unique Variants	224649
Samples	773098	Fusions	8931
Mutations	405271	Genomic Rearrangements	7503
Papers	14819	Whole Genomes	2556

Whole Genome: 21,365 samples
~ 1000 cancer cell lines



Gene Expression Omnibus

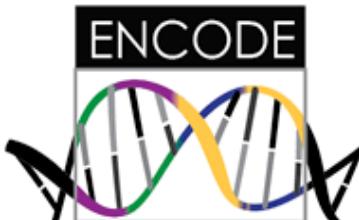
- 471,624 Cancer microarrays
- 7,150 Cancer DNA methylation arrays experiments



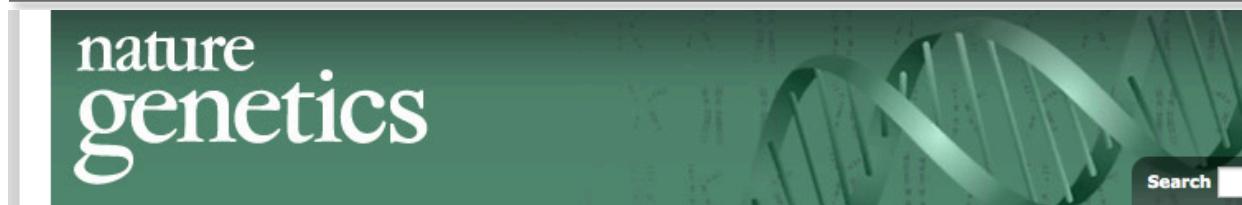
- 947 cancer cell lines
- 36 cancer types
- Targeted sequencing of 1,651 genes

1000 Genomes

A Deep Catalog of Human Genetic Variation



The Cancer Genome Atlas Pan-Cancer Analysis Project



Journal home > Focuses > Focus on TCGA Pan-Cancer Analysis

Journal content

- + [Journal home](#)
- + [Advance online publication](#)
- + [Current issue](#)
- + Archive**
- + [Focuses and Supplements](#)
- + [Press releases](#)
- + [Free Association \(blog\)](#)

Journal information

- + [Guide to authors](#)
- + [Online submission](#)
- + [Permissions](#)
- + [For referees](#)
- + [Contact the journal](#)
- + [Subscribe](#)
- + [About this site](#)

NPG services

- + [Authors & Referees](#)
- + [Advertising](#)
- + work@npg
- + [naturereprints](#)

Focus

Focus on TCGA Pan-Cancer Analysis



Focus issue: [October 2013 Volume 45, No 10](#)

- > [Contents](#)
- > [Foreword](#)
- > [Editorial](#)
- > [Analysis](#)
- > [Commentaries](#)

Genomic alterations in diverse cell types at different sites in the body give rise to hundreds of different forms of cancer and the ways in which these changes give rise to tumors with different biology, pathology and treatment strategies are beginning to be characterized. The Cancer Genome Atlas Research Network has catalogued the aberrations in the DNA, chromatin and RNA of the genomes of thousands of tumors relative to matched normal cellular genomes and have analyzed their epigenetic and protein consequences. Here, the Pan-cancer initiative examines the similarities and differences among the genomic and cellular alterations found in the first dozen tumor types to be profiled by TCGA. This first look across cancer offers new tools in genomics and bioinformatics and the prospect of repurposing targeted therapies directed by the molecular pathology of the tumors in addition to their clinical classification.

Editorial

[top](#)

Focus on TCGA Pan-Cancer Analysis

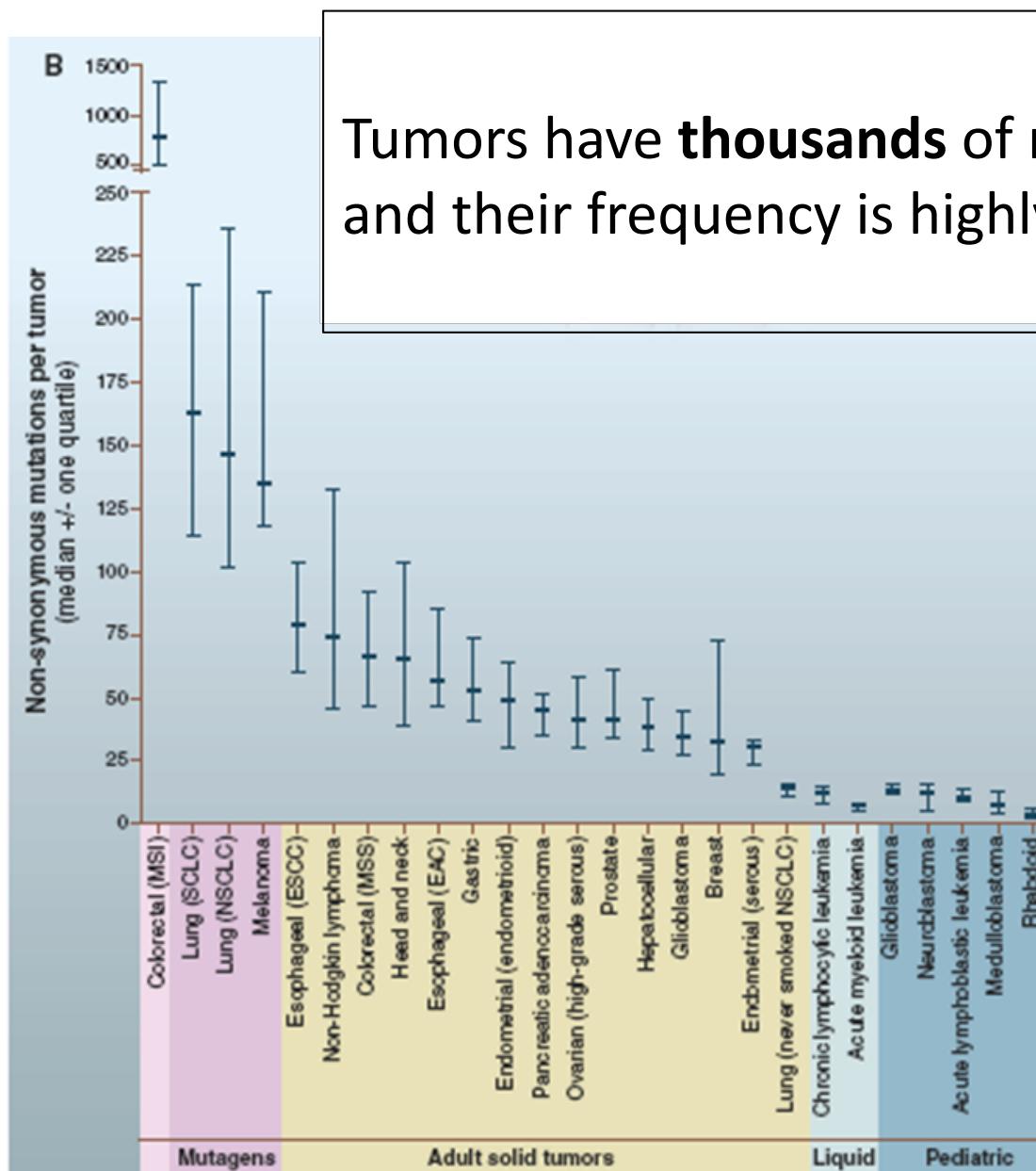
Targeting molecular tumor types p1103

doi:10.1038/ng.2780

In this issue, the Focus on Pan-Cancer Analysis examines the similarities and differences among the genomic and cellular alterations found in the first dozen tumor types to be profiled by The Cancer Genome Atlas (TCGA) Research Network. This first look across cancers offers new tools in genomics and bioinformatics and the prospect of repurposing targeted therapies to be directed by the molecular pathology of tumors in addition to their clinical classification.

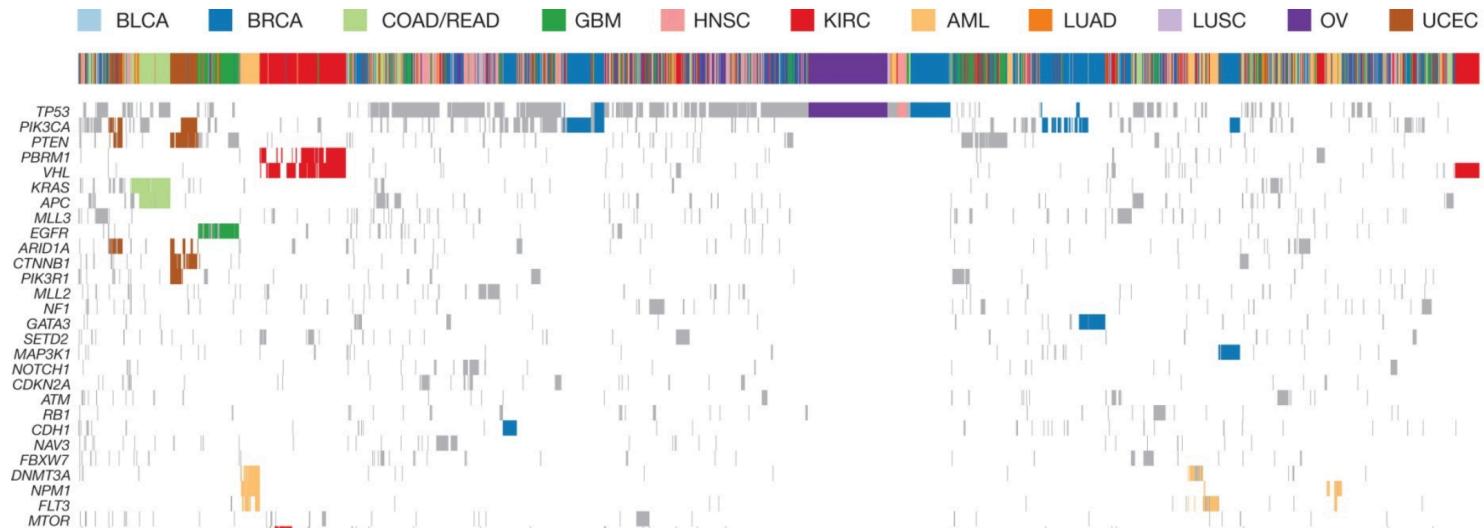
Nature Genetics October 2013 Volume 45, No 10

Cancer Genome Landscape

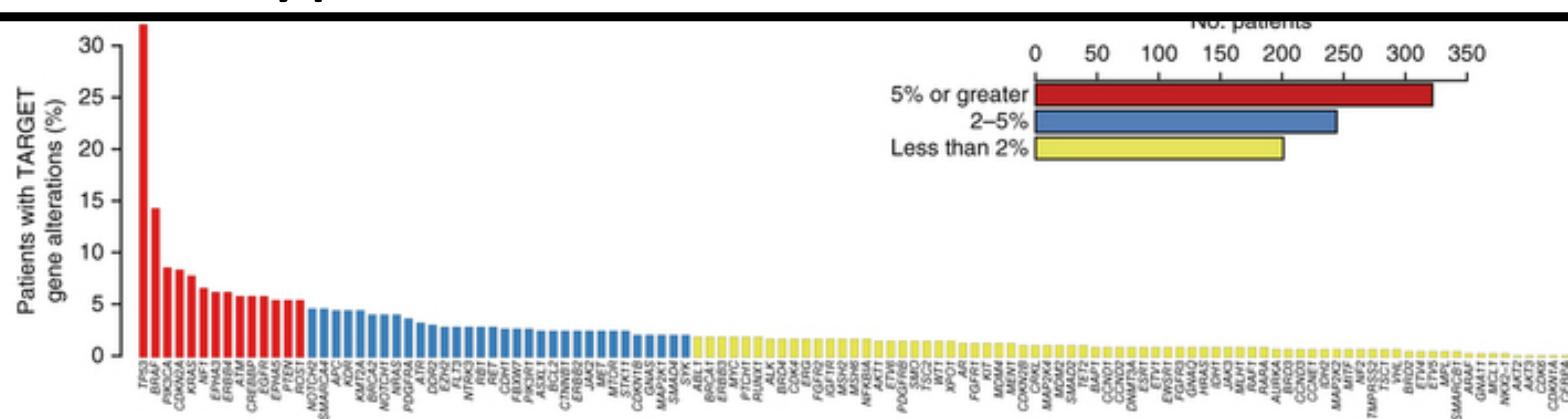


Tumors have **thousands** of molecular alterations and their frequency is highly **heterogeneous**.

Top genes frequently mutated in cancer



It is important to identify and understand the molecular landscape for each patient beyond the tumoral type



PERSONALIZED MEDICINE

- Why sequence Genomes?
 - Understand basic biological processes
 - Understand how individuals differ from one another
 - Understand how species differ from one another
 - Understand basis of disease
 - Improve human health
- Why you might?
 - Might want to know sensitivity to medication (Pharmacogenomics)
 - Might want to know if you are likely to get certain diseases
 - Just curious
- Why you might not?
 - Might not want if you are likely to get certain diseases (eg: incurable diseases)
 - Most diseases are complex: we don't really know enough to make good use of information
 - Worry about genetic privacy/discrimination by employers, insurance companies.

Personal Genomes

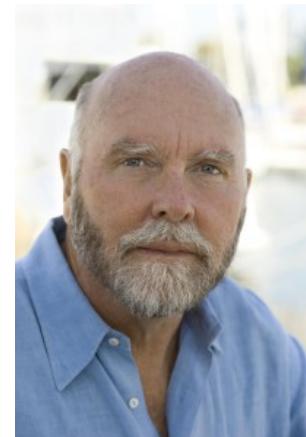


Table 1. Individual genomes that have been sequenced and published

Project	Technology	Paired end	SNPs; short Indel	SVs	New sequence	Fully phased genotyping	Reference
Reference	Sanger	No	NA	NA	NA	NA	Lander et al. 2001; Collins et al. 2003
European-Venter	Sanger	Yes	3 million; 0.3 million	0.2 million (>1000 bp)	1 M	Limited	Levy et al. 2007
European-Watson	454	No	3 million; 0.2 million	Limited	No	No	Wheeler et al. 2008
European-Quake Asian	Helicos Illumina	No Partially	3 million 3 million; 0.1 million	Limited 2700 (>100 bp)	No No	No No	Pushkarev et al. 2009 Wang et al. 2008
HapMap sample; Yoruban 18507	Illumina	Yes	4 million; 10,000	100	No	No	Bentley et al. 2008
HapMap sample; Yoruban 18507	SOLiD	Partially	4 million; 0.2 million	5500 (unknown definition)	No	No	McKernan et al. 2009
Korean	Illumina	Yes	3 million	Limited	No	No	Ahn et al. 2009
Korean-AK1	Illumina	Yes	3.45 million; 0.17 million	~300 CNVs	No	No	Kim et al. 2009
Three human genomes	Complete genomics	Yes	3.2–4.5 million; 0.3–0.5 million	Limited (50,000–90,000 block substitutions)	No	Limited	Drmanac et al. 2009
AML genome and normal counterpart	Illumina	No	3.8 million; 700	Limited	No	No	Ley et al. 2008
AML genome	Illumina	Yes	64	Limited	No	No	Mardis et al. 2009
Melanoma genome	Illumina	Yes	32,000; 1000	51	No	No	Pleasant et al. 2010a
Lung cancer genome	SOLiD	Yes	23,000; 65	392	No	No	Pleasant et al. 2010b

Fifteen genomes have been sequenced from 13 individuals in addition to the original reference sequence. The HapMap cell line NA18507 has been sequenced independently three times. For the purposes of this tabulation, genomes deduced from both normal and disease are counted as one sequence. (NA) Not applicable.

Impact of Cancer Genomics on Medicine

- **Enable Prevention**
 - Understanding the underlying etiology (strategy)
- **Facilitate early detection**
 - Identify risk alleles / genomic events for screening
 - Early events may be detectable in serum or by imaging
- **Guide evidence-based intervention**
 - Stratify high vs low risk patients to treat or not
 - Identify new therapeutic targets for drug discovery
 - Inform selection of the right patient for the right drug
 - Define combination strategies

Impact of Cancer Genomics on Medicine

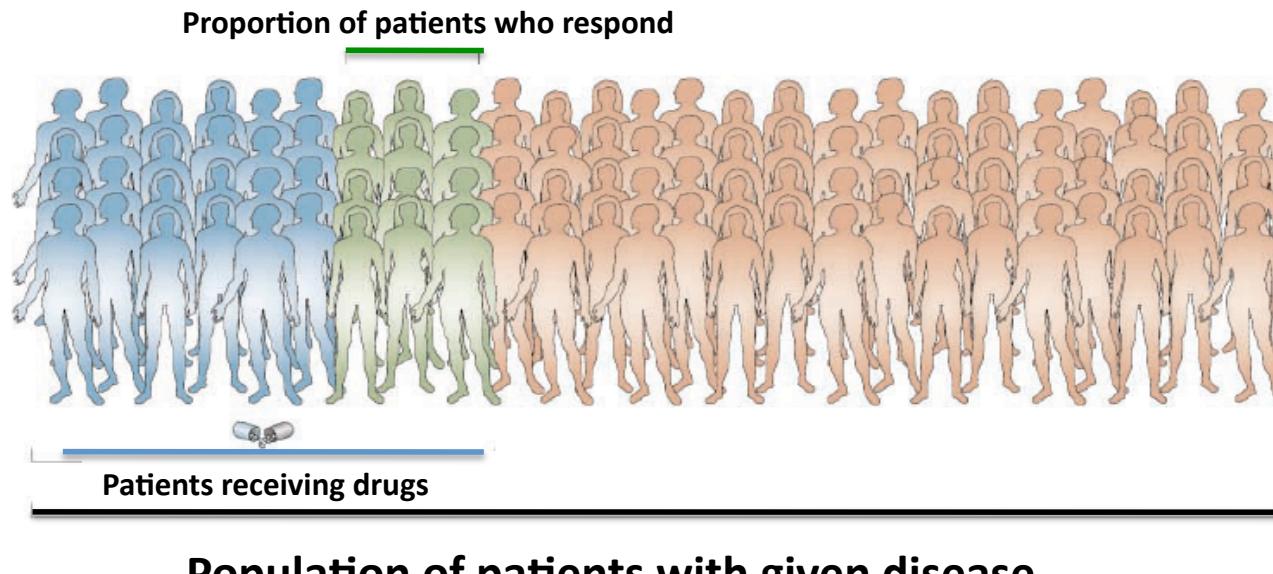
- **Predisposition testing** – determines who is at risk for a disease
 - BRCA1/BRCA2: screening in women with a significant family history may help predict their risk for breast or ovarian cancer.
 - Type 2 diabetes: screening individuals with impaired glucose tolerance for TCF7L2 may help identify those who are at risk.

Time Magazine May 27 2013

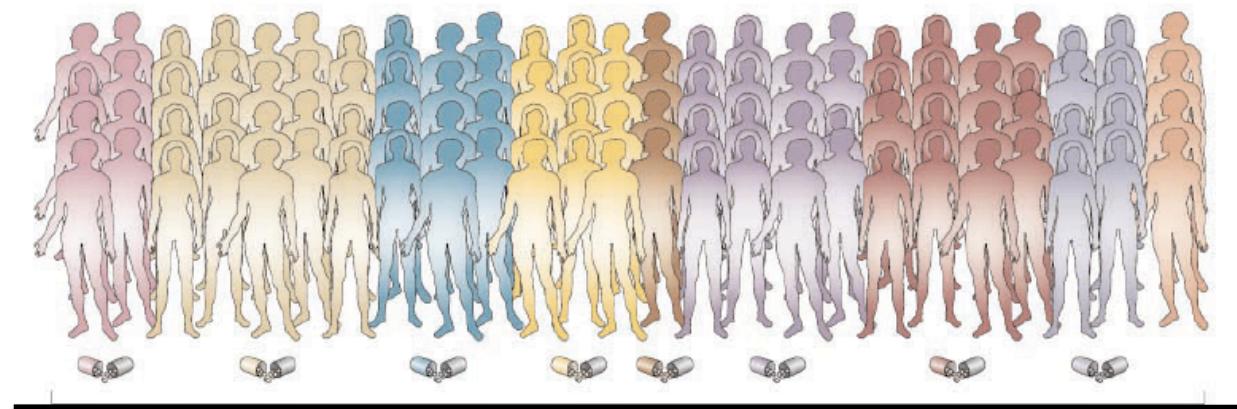


“Her preventive mastectomy raises important issues about genes, health and risk”

Current status of drug development research

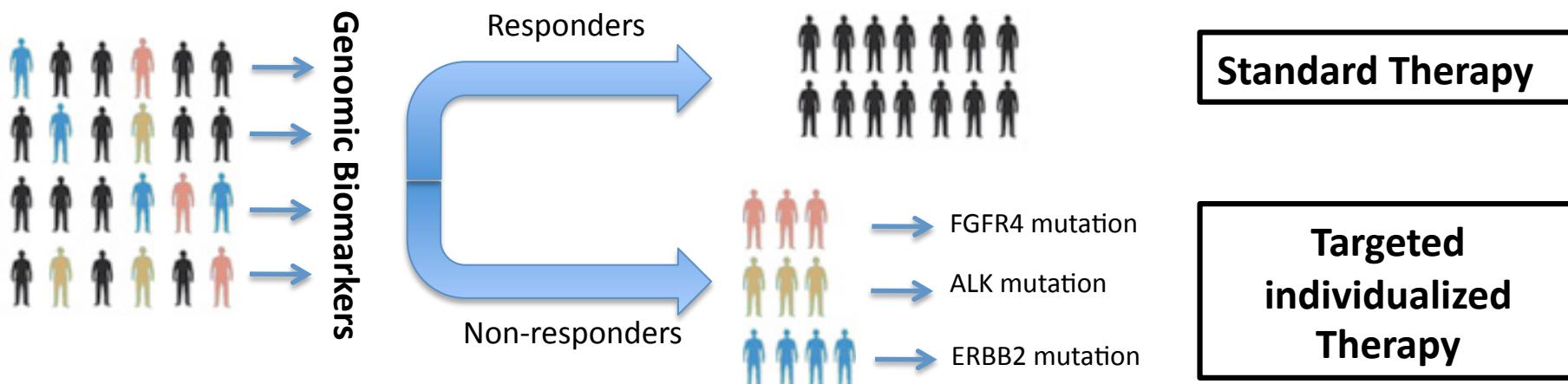


Ideal future objective of drug development research

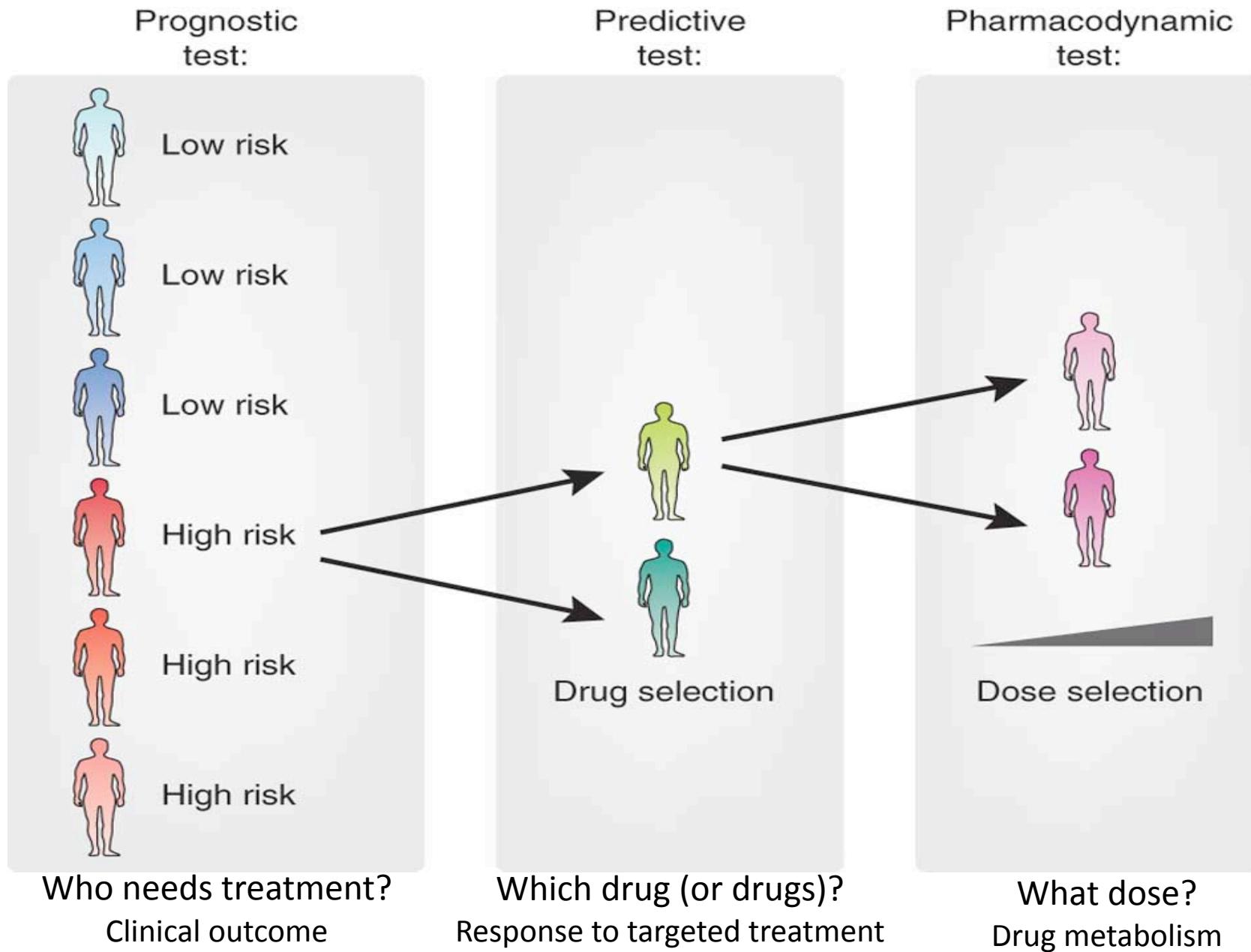


The Goal of Cancer Personalized Medicine

- To fulfill the promise of delivering the right dose for the right indication to the right patient at the right time.
- Personalized medicine uses an individual's genetic profile and individual information to guide decisions made in regard to the prevention, diagnosis, and treatment of cancer.



Type of biomarker



Genetic Biomarkers and new targeted therapies

Drug	Company	Type	Target	Status
► ARQ 736	ArQuie	small molecule	BRAF	Phase I
► Selumetinib	Array BioPharma	"	MEK	Phase II
► PD-0325901	Pfizer	"	MEK	Phase I
► PX-866	Oncothyreon	"	PI3K	Phase II
► BEZ235	Novartis	"	PI3K	Phase I
► BKM120	Novartis	"	PI3K	Phase II
► Tivantinib	ArQuie	"	MET	Phase II

VEGFR-2

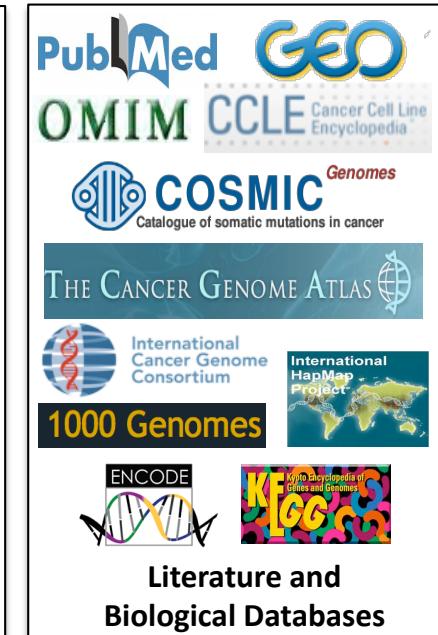
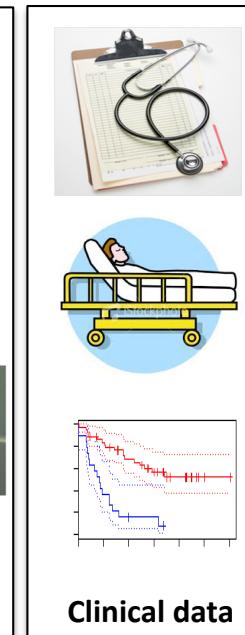
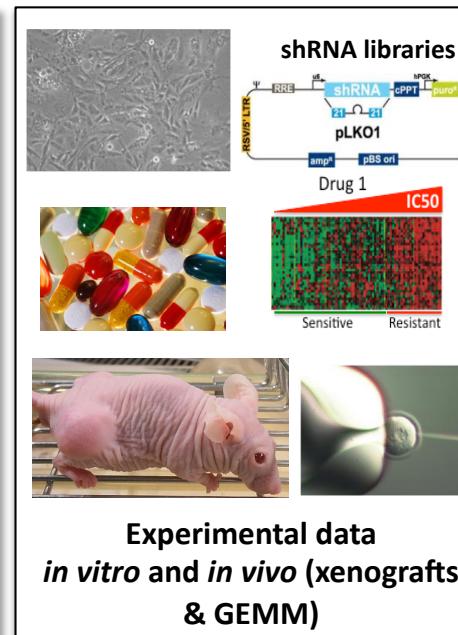
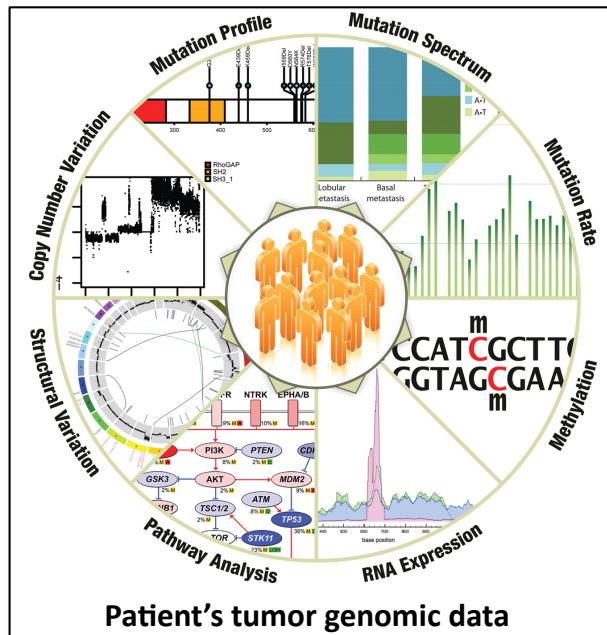


55 Pharmacogenomic Biomarkers in Oncology (FDA Approved)

► Ramucirumab	ImClone Systems	"	VEGFR-2	Phase II
► AMG 386	Amgen	biologics (peptibody)	Tie-2R	Phase II
► GL-ONC1	Genelux	biologics (oncolytic virus)	Tumoral cells	Phase I/II
► ColoAd1	PsiOxus	"	"	Phase I/II
► NV1020	Medigene	"	"	Phase II
► Reolysin	Oncolytics	"	"	Phase I/II
► JX594	Jennerex	"	"	Phase I/II

Integrative Genomics

Discovery of novel oncogenes, tumor suppressor genes, oncogenic pathways & Biomarkers



Bioinformatic analyses + Data warehouse/Framework



Variant prediction

Gene/protein function prediction

Pharmacogenomics:
Druggable targets

Application → Clinical interpretation → Personalized Medicine

Precision Medicine challenges

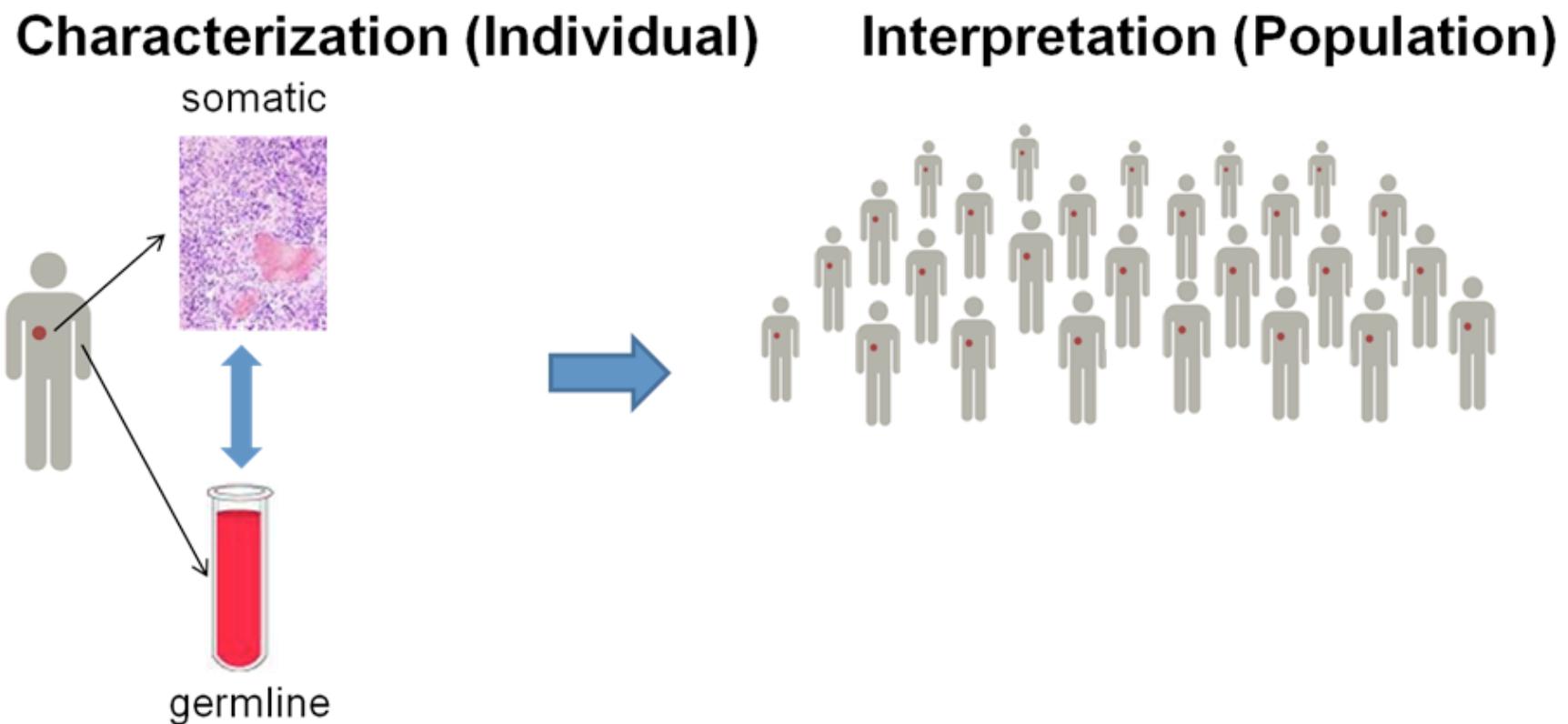
Now the molecular landscape has been defined for many tumor types

- A few cancer genes (drivers) are mutated in a high proportion of tumors of a given type (> 20%), most are mutated at intermediate frequencies (2-20%) (long-tail) (Lawrence et al (2014) Nature)
- We need to associate these alterations with current therapies in the appropriate clinical context.
- Cancer therapeutic options are still very limited and most patient acquire resistance to the treatment.
- The ability to harness tumor genetic information for its full clinical potential has only recently become manifest (Garraway, JCO, 2013).

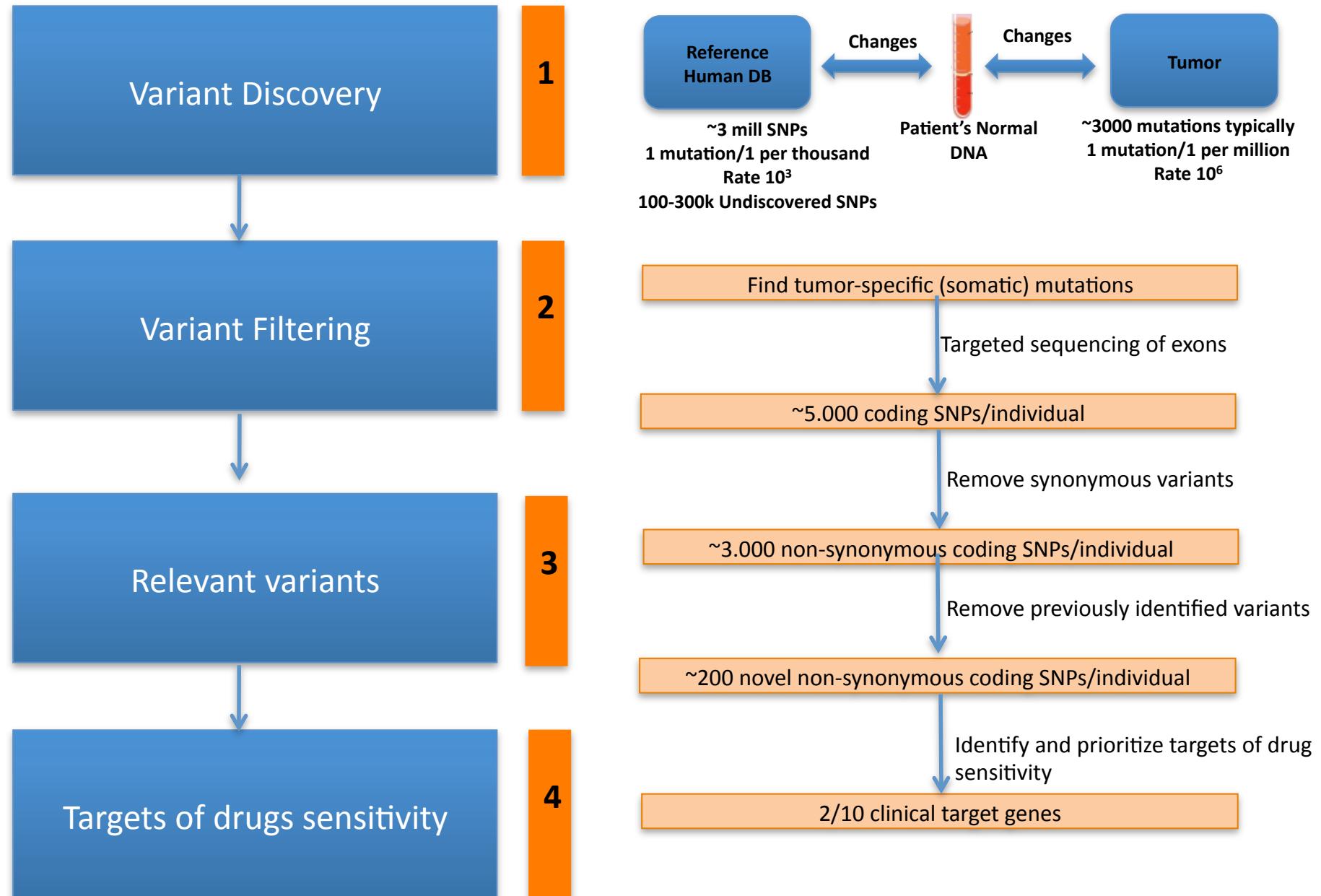
New approaches must be developed to propose new therapeutic strategies

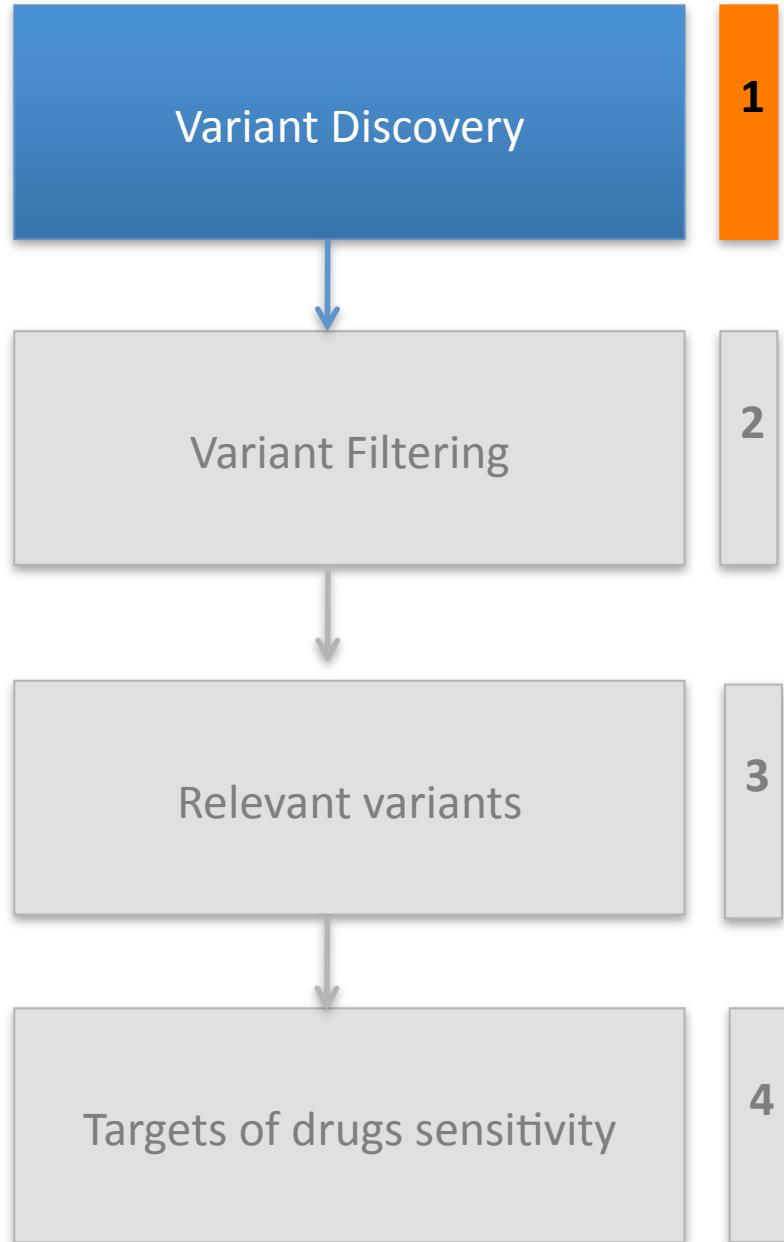
METHODOLOGY

Cancer Genome Analysis Tools



Variant analysis in exome sequencing data





Find somatic mutations tumor-specific

1.- Variant Discovery

Methodologies:

- Mapping and alignment algorithms (BLAT, BWA, Bowtie, TMAP)
- Public and home-made pipelines for NGS analysis (GATK, RubioSeq-CNIO)
- Sequencing technologies are affordable. ~3000 eur/~1 week (exome).

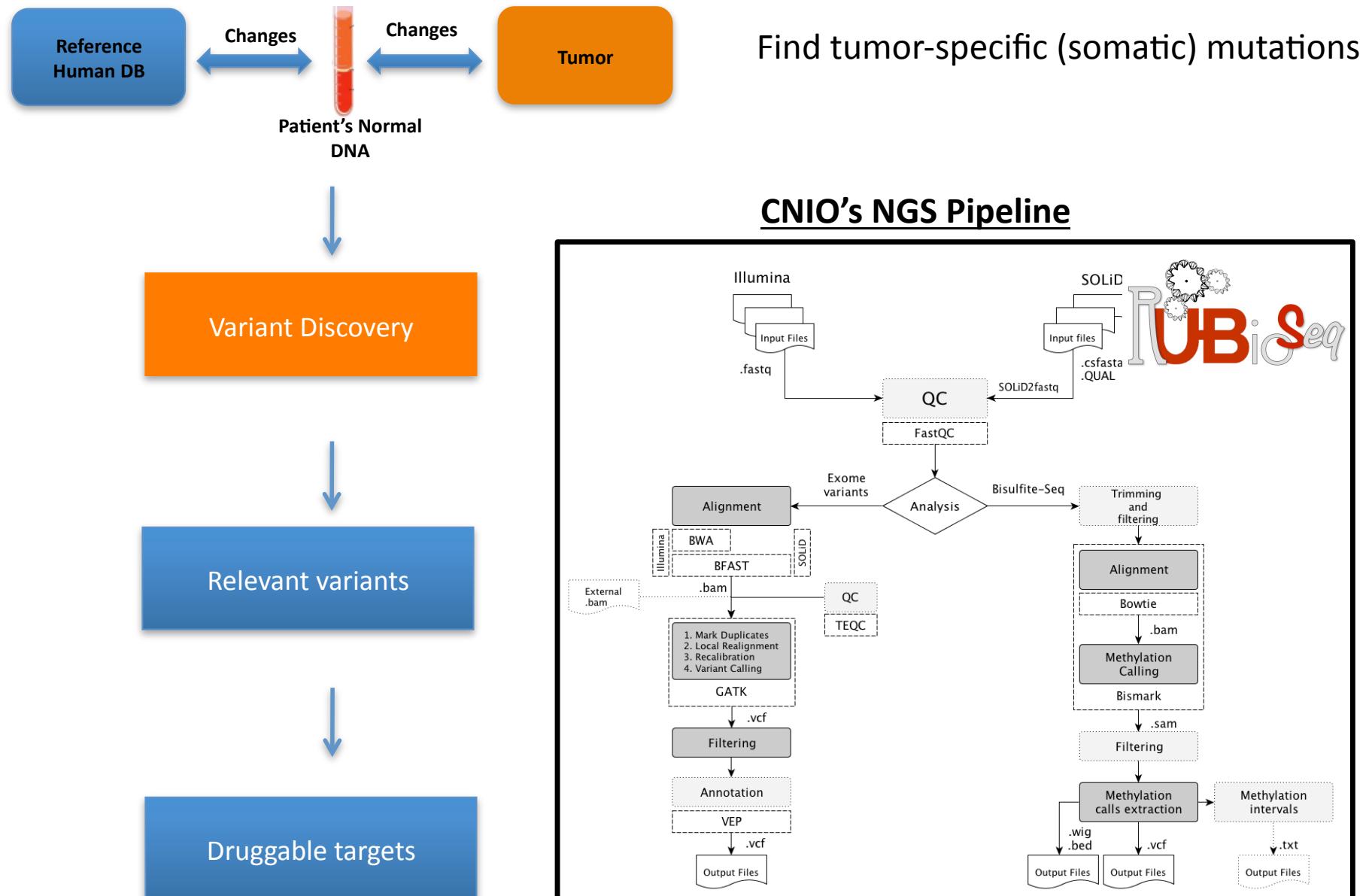
Limitations:

- Lack of technology standards (genomics, informatics, emerging technologies)
- Mapping and alignments algorithms produce different results.
- Whenever a novel variant is identified, it will still have to be verified due to this false positive rate.
- Indels as CNVs and SVs are difficult to detect.

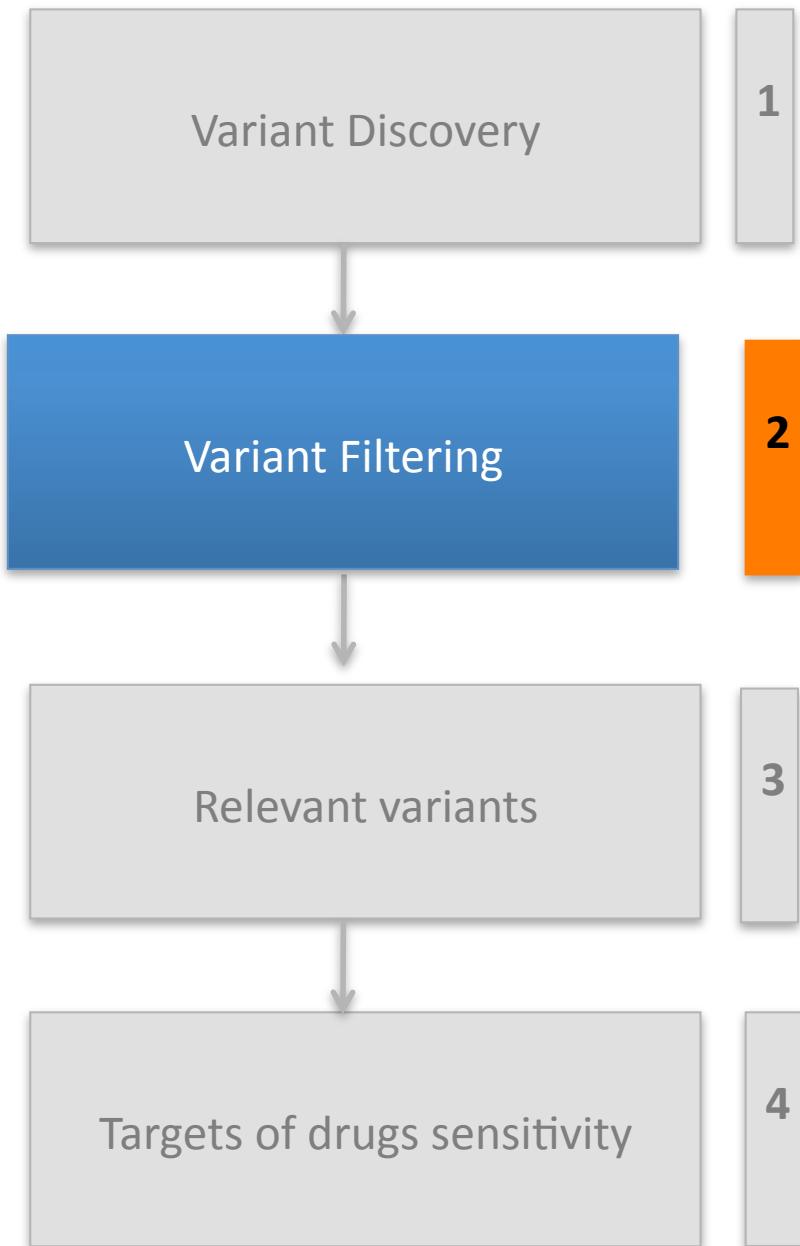
Challenges:

- Processing large scale genomic data.
- Decrease the error rate (~1 error/100Kb means 30.000 errors per genome).
- Detection of rare and novel variants will require increased confidence in the variant call.
- New algorithms for calling indels.
- Improve QC metrics

Variant analysis in exome sequencing data



Miriam Rubio, Gonzalo Gómez, David Pisano.
CNIO Bioinformatics Unit



Elimination of variants that do not segregate with disease and they don't have a functional impact.

2.- Variant Filtering

Methodologies:

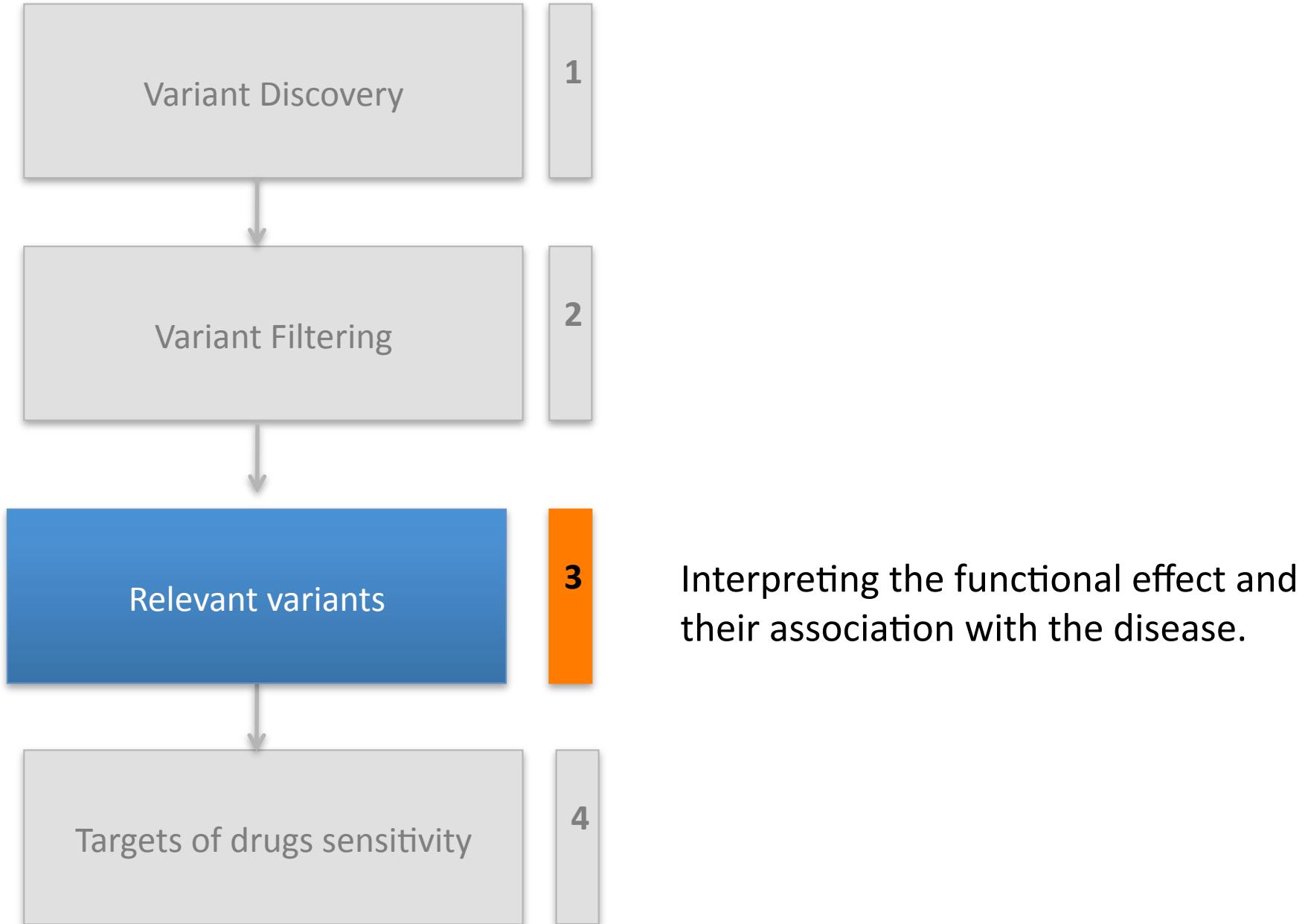
- Gene structure: Elimination of synonymous/non-coding variant.
- Control variants: Elimination of dbSNP, HGMD, HapMap, dbVAR, DGV variants, 1000 Genomes Project.
- Computational methods to predict deleterious missense variants. The prediction algorithms input features generally include amino acid sequence, protein structure and evolutionary information: (SIFT, PolyPhen, MutationAssessor, Condel, SNPEffect, SNPs3D, FIREDB, FireStar: validated annotations of binding sites and analysis of mutations at the 3D level).

Limitations:

- GWAS are providing new insights, but only a limited number of variants have been characterized, and understanding the functional relationship between associated variants and phenotypic traits is difficult.
- Prediction methods do not provide any information about the pathophysiology of the diseases and so experimental tests are required to validate genetic predictions

Challenges:

- To filter or not to filter? Optional
- Data management, retrieval and quality control.



3.- Prioritize variants (genes)

Methodologies:

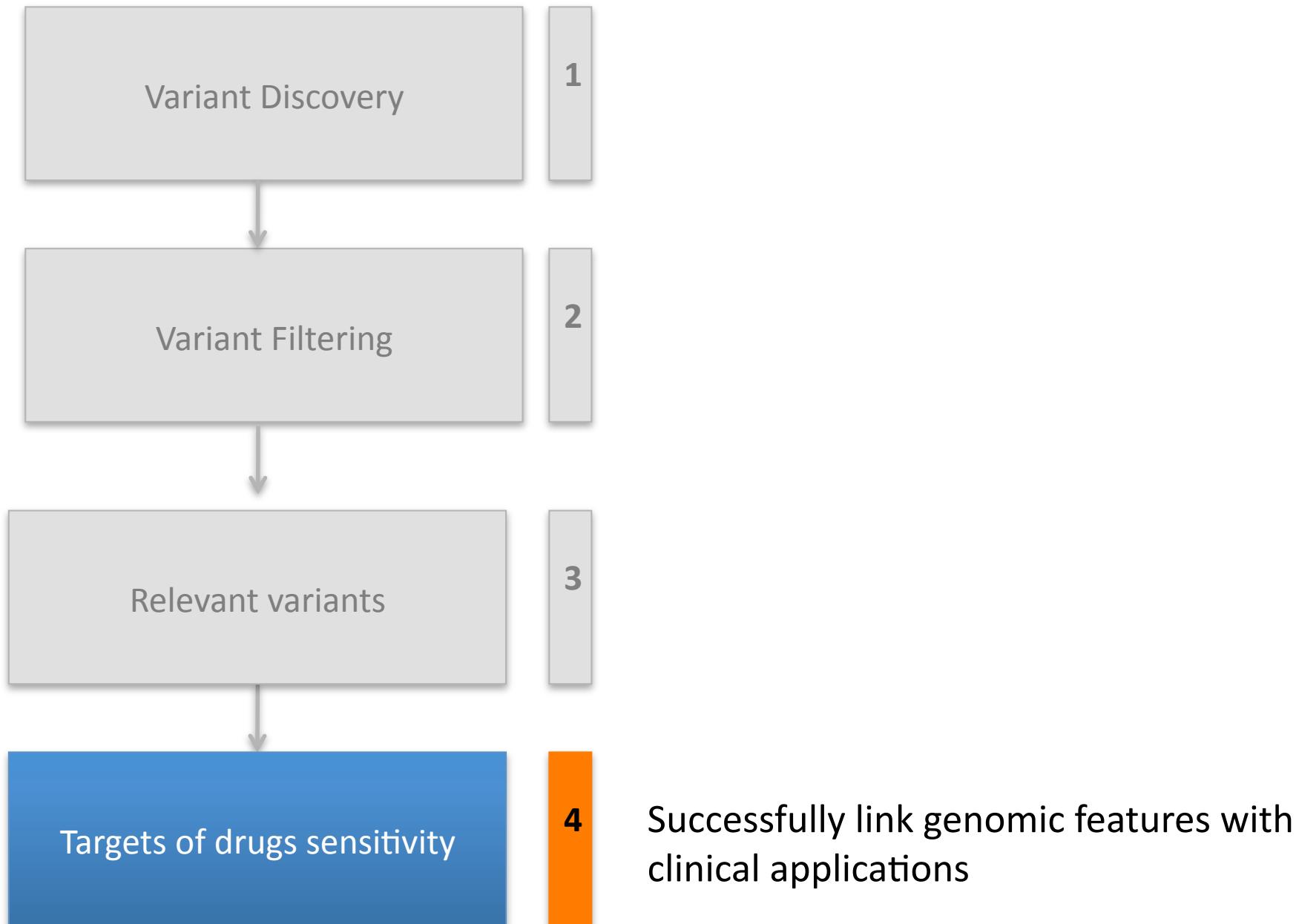
- Prioritize variants predicted as damaging.
- Literature Annotation: UCSC, Ensembl, Cancer Genes, OMIM, Text-mining. COSMIC
- Reference Cancer Genome (by recurrence): ICGC and TCGA projects.
- Evolutionary conservation: Prioritize variants highly conserved across species.
- Integration of genomic data resources: Expression, CNVs, Proteomics,
- Guilty-by-association: Genes involved to the biological process of interest.
- Pathway level: Identification of significantly altered gene sets and/or pathways using KEGG or other DBs (PARADIGM, Dendrix).

Limitations:

- Understanding of genomic variation data is limited and complex.
- There aren't tools for disease prediction.
- Different tools but they aren't integrated in a useful and guided pipeline.
- New methods are needed to evaluate the impact of insertion, deletion and synonymous variants.
- Predict the impact of non-coding variants affecting (regulatory regions and splicing sites).

Challenges:

- To manage large quantities of pre-processed data.
- Interpreting the functional effect and the impact of genomic variation.
- Integrating systems data to relate complex genetic interactions with phenotypes.
- Analyze biomedical DBs to build relationship between diseases, genes, mutations, drugs and pathways.



4.- Druggable targets

Methodologies:

- Drug-single gene association or sometimes pathways.
- Literature
- Cancer Cell line Encyclopedia and Sanger Resources.



Limitations:

- one-variant, one-phenotype approach is inefficient.
- Gene-gene interactions
- Environmental interactions
- There aren't integration with any external knowledge sources or inform the biology behind the interactions.
- Lack of common technology platforms to enable the sharing of information and transfer to clinical application.

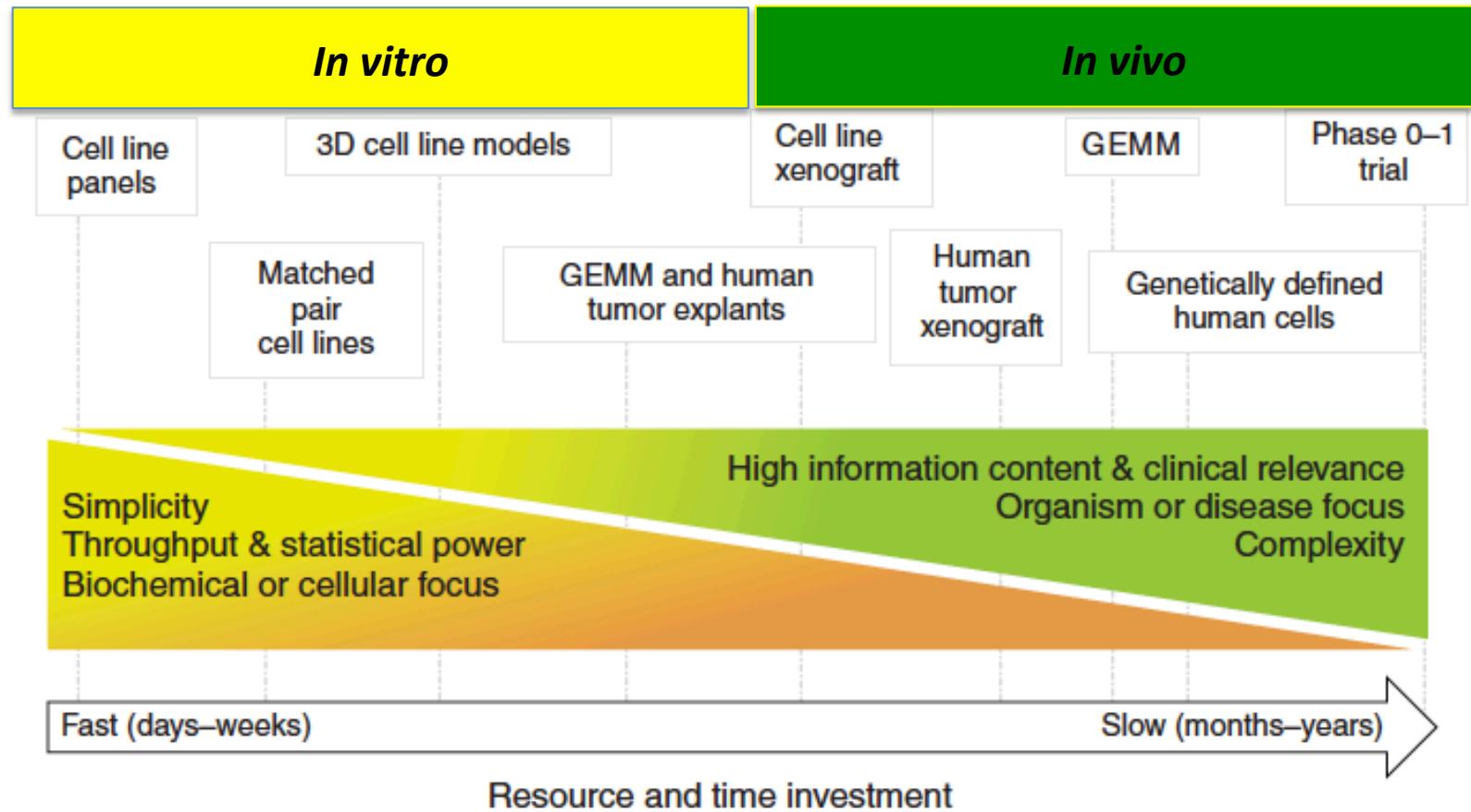
Therapeutic Targets Database



Challenges:

- Developing methods to integrate drug sensitivity with genomic data.
- Developing methods that combine multiple data sources and multi-factor predictions.
- Translating these discoveries into medical practice.
- Tools for predicting drug–target or drug–gene interactions will be essential.
- Prospective gene-stratification hypotheses need to be generated for future trials and will require new bioinformatics methods.
- Lack of common vocabularies

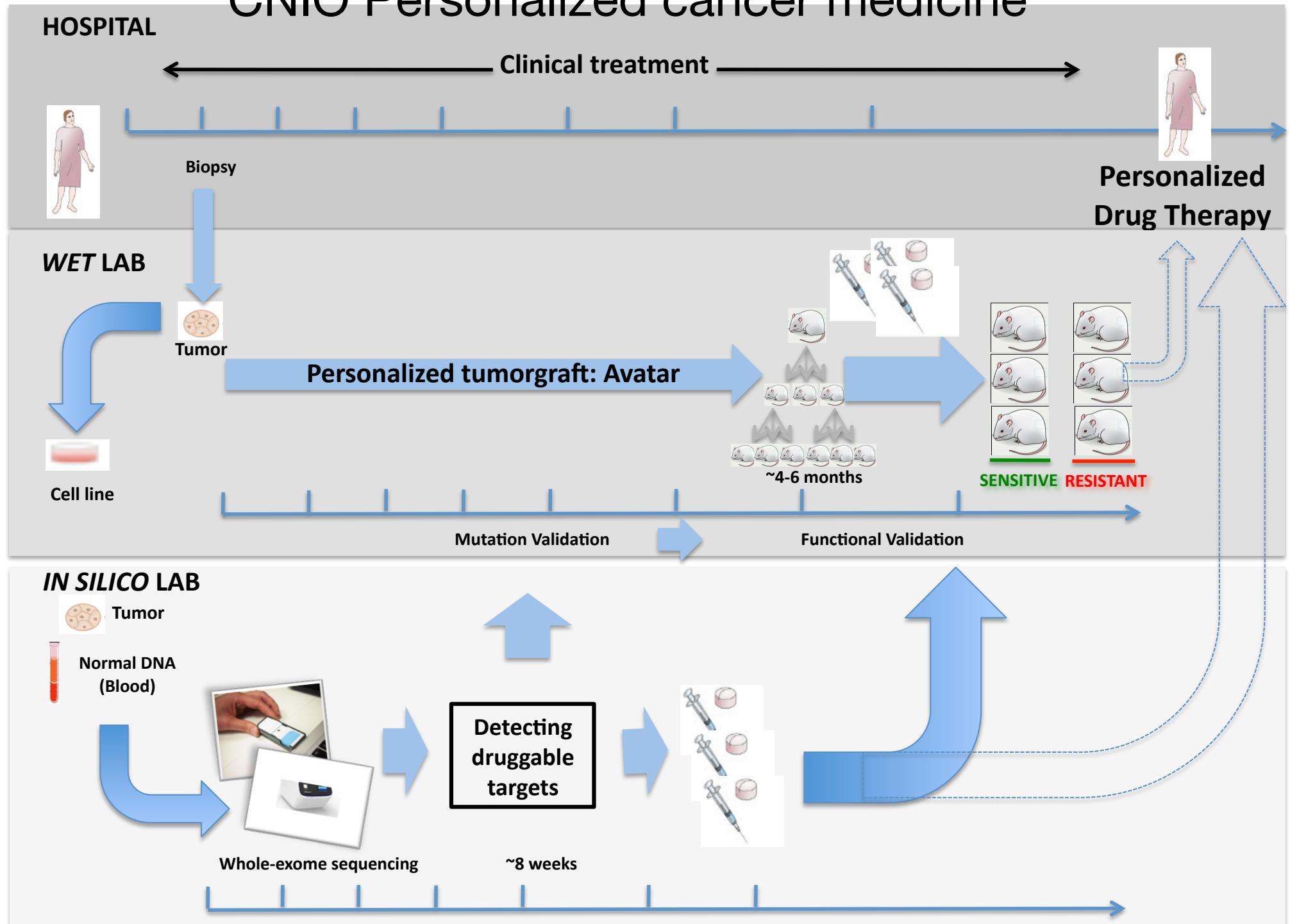
5. Great Mutation: Is it Functional?



- Fast
- High-throughput validation of multiple candidates
- More predictive
- GEMM allow to identify initiators cancer genes

CNIO' S PERSONALIZED MEDICINE PROTOCOL

CNIO Personalized cancer medicine



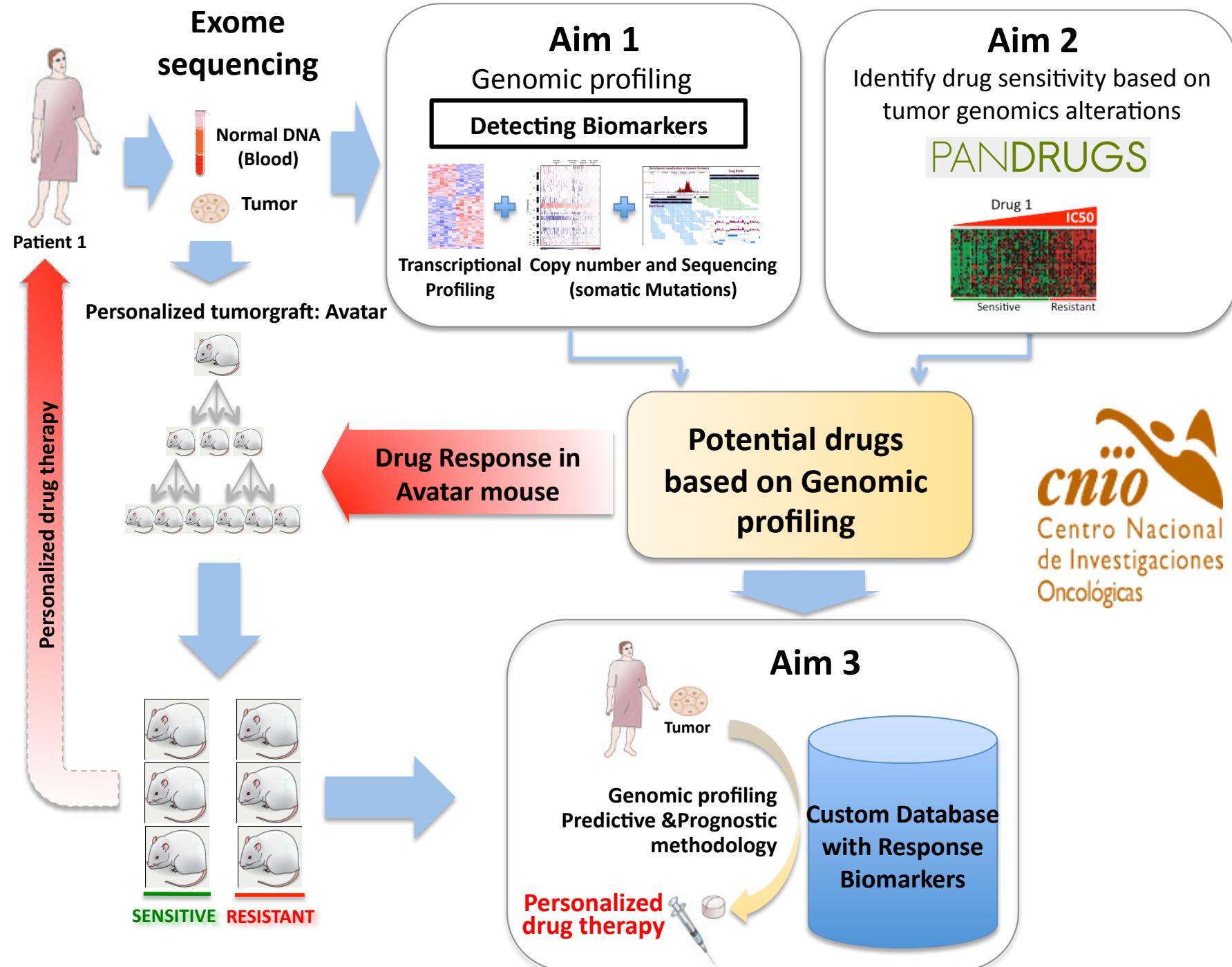
In vivo Pre-clinic platform: Personalized Tumorgrafts (**Avatar**)

- Avatar mouse models are generated by direct engraftment of tumor samples from the patients into immunocompromised mice.
 - Avatar recapitulate the biological characteristics of the disease of origin and its cellular heterogeneity.
-
- *In vivo* platform that provides the opportunity to test proposed strategies.
 - They are susceptible to cryopreservation – access to “unlimited” amount of tumor tissue.



Applications:

- To test new drugs activity
- To validate genomic hypothesis (Biomarkers discovery)
- To generate new pharmacogenomics association.
- To predict drug response.
 - All EGFR mutant patients will respond to EGFR inhibitors?



Personalizing cancer treatment in the age of global genomic analyses: *PALB2* gene mutations and the response to DNA damaging agents in pancreatic cancer

Maria C. Villarroel*, N.V. Rajeshkumar*, Ignacio Garrido-Laguna, Ana De Jesus-Acosta, Siân Jones, Anirban Maitra, Ralph H. Hruban, James R. Eshleman, Alison Klein, Daniel Laheru, Ross Donehower, and Manuel Hidalgo

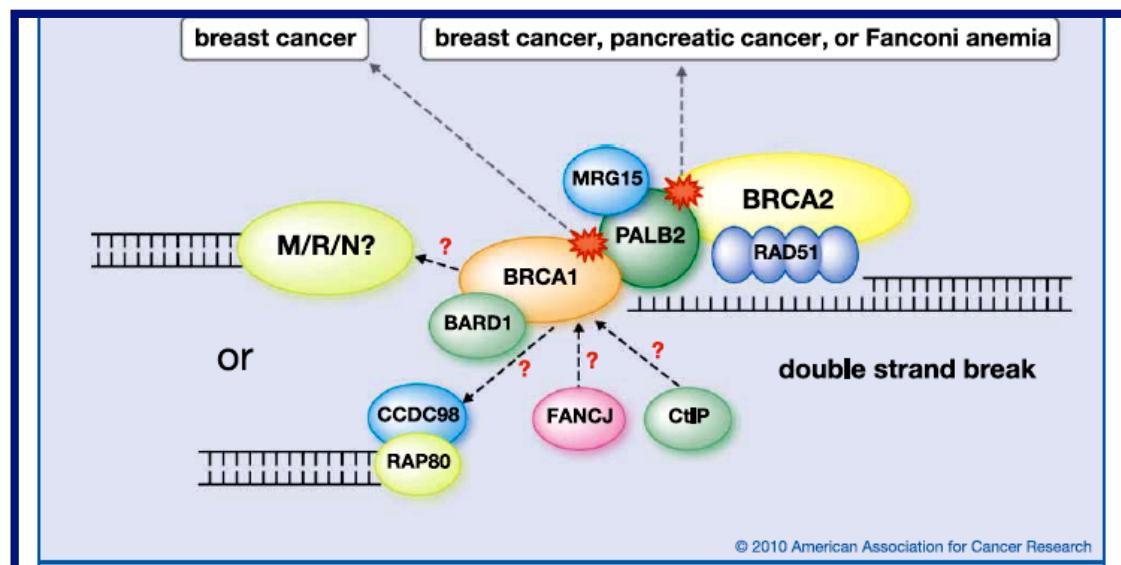
The Sidney Kimmel Comprehensive Cancer Center and the Sol Goldman Pancreatic Cancer Research Center, The Johns Hopkins University School of Medicine, Baltimore, MD 21231

- 61yo male
- Pancreatic adenocarcinoma pT3N1M0
 - Surgery: Fresh tumor specimen was obtained for exome sequencing and for Avatar generation.
 - Adjuvant chemotherapy: Gemcitabine
 - DFS: 4 months
 - Loco -regional disease progression.

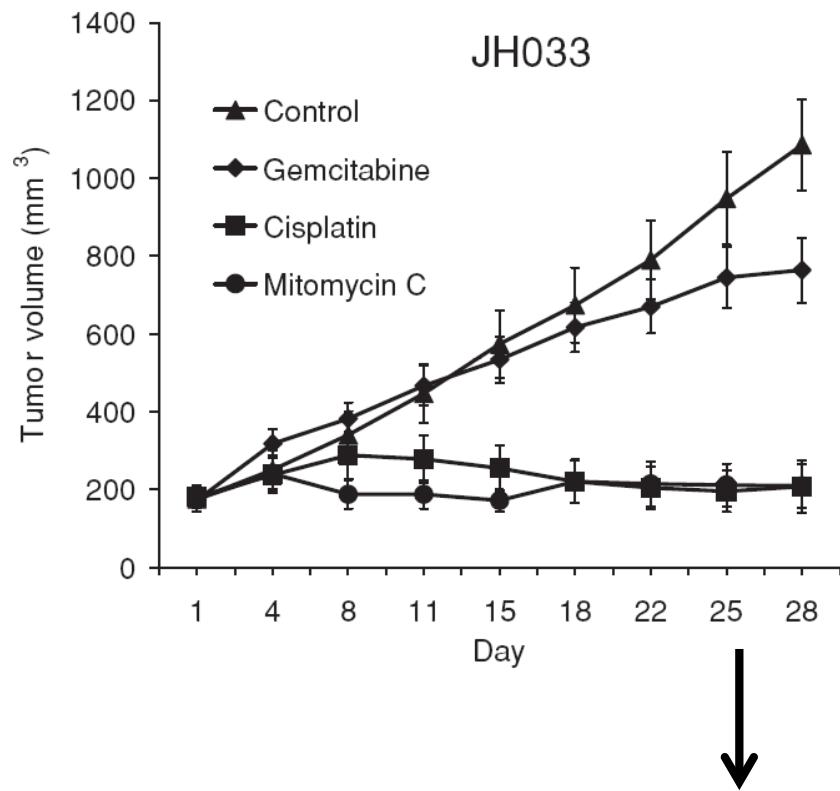
- Exome sequencing detected : Doble mutation in PALB2 (*Partner and Localizer of BRCA2*)



Alteration in the double strand DNA Break Repair Mechanism



Tischkowitz and Xia, (2010), Cancer Res, 70
(19): 7353-9)



Avatar Model was
tested with
different Alkylating
Agents



- Patient started treatment with Mitomycin C
- Maintained partial response for over 22 months.

Research/Diagnostics/Treatment – *Personalized medicine*

Exome sequencing

Illumina



Whole-Exome Sequencing
~21000 coding genes

+

Patient-Derived Xenografts (PDX) models



Targeted sequencing

1) Ion AmpliSeq Cancer Panel

ABL1	EZH2	JAK3	PTEN
AKT1	FBXW7	IDH2	PTPN11
ALK	FGFR1	KDR	RB1
APC	FGFR2	KIT	RET
ATM	FGFR3	KRAS	SMAD4
BRAF	FLT3	MET	SMARCB1
CDH1	GNA11	MLH1	SMO
CDKN2A	GNAS	MPL	SRC
CSF1R	GNAQ	NOTCH1	STK11
CTNNB1	HNF1A	NPM1	TP53
EGFR	HRAS	NRAS	VHL
ERBB2	IDH1	PDGFRA	
ERBB4	JAK2	PIK3CA	



ion torrent
by life technologies®

HM
CENTRO INTEGRAL ONCOLÓGICO
CLARA CAPALI
HOSPITALES

2800 mutations / 50 genes

2) Ion AmpliSeq™ Colon and Lung Cancer Panel

KRAS, EGFR, BRAF, PIK3CA, AKT1, ERBB2, PTEN, NRAS, STK11, MAP2K1, ALK, DDR2, CTNNB1, MET, TP53, SMAD4, FBXW7, FGFR3, NOTCH1, ERBB4, FGFR1, FGFR2

500 mutations/22 genes

3) Ion AmpliSeq™ BRCA1 and BRCA2 Panel

Coding regions of the tumor suppressor genes BRCA1/2

4) Ion AmpliSeq™ Comprehensive Cancer Panel

All-exon coverage / 409 genes

Personalized Medicine



Whole-Exome Sequencing
~21000 coding genes
+
PDX (Avatar model)



- **25** patients enrolled.
- **23** patients with advanced cancer had **exome analysis** performed.
 - Results were only obtained for 23 patients due to the clinical worsening condition of the remaining two.
- Tumor was implanted to create an **Avatar model** from 14 patients and **10** succeeded.

Patients, treatments and outcome

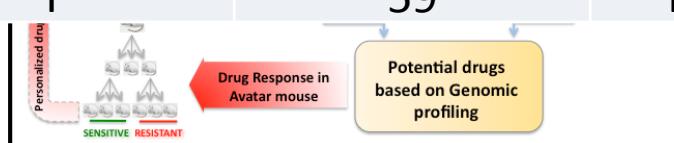
Patient #	Primary tumor	Putative Target on NGS	Avatar Best Treatment	Patient Tailored treatment	Best Response (RECIST)	Time on Treatment (months)	Present Status
1	Neuroendocrine tumor	CREB3L3 mutation	No engraftment	Sandostatin + Metformine	SD Complete metabolic response by PET	18+	On treatment
2	Glioblastoma	NF1 mutation	Rapamycin + erlotinib	Everolimus + Erlotinib + Bevacizumab	PD	3	Dead
3	Hypothalamic glioma	PTPRC mutation, KIF5B-RET Fusion	No engraftment	Irinotecan + Pemetrexed + Bevacizumab Nab-paclitaxel + everolimus	1 st : SD 2 nd : PR 3 rd : PR	18+ 13 4	Dead
5	Uveal Melanoma	STK11 Whole Gene Deletion	No engraftment	-	1 st : CR 2 nd : PR 3 rd : SD	13 4 2+	Other treatment
10	Glioblastoma	No target	No engraftment	-	1 st : PR 2 nd : PR	6 3+	Dead
12	NSCLC	EGFR mutation	No engraftment	Erlotinib	PR	24+	On treatment
13	Glioblastoma	No target	No engraftment	-	1 st : PR 2 nd : PR	6 3+	On treatment
14	NSCLC	EGFR mutation	No engraftment	Erlotinib	PR	24+	On treatment
15	NSCLC	PTPRC mutation, KIF5B-RET Fusion STK11 Whole Gene Deletion	-Irinotecan + Pemetrexed + Bevacizumab -Nab-paclitaxel + everolimus	1 st : Irinotecan + Pemetrexed + Bevacizumab 2 nd : Nab-paclitaxel + everolimus 3 rd : Sunitinib	1 st : CR 2 nd : PR 3 rd : SD	13 4 2+	On treatment
16	NSCLC	EGFR	-Cisplatin + Gemcitabine -Nab-paclitaxel -Everolimus	1 st : Cisplatin + Gemcitabine 2 nd : Nab-paclitaxel + everolimus	1 st : PR 2 nd : PR	6 3+	On treatment
17	SCLC	No target	-Irinotecan -Nab-paclitaxel	1 st : Irinotecan 2 nd : Nab-paclitaxel	1 st : PR 2 nd : SD	6 4	Dead
20	Duodenal	NRAS and PIK3R1 mutation	-Gemcitabine + Everolimus -Eribulin -Irinotecan + cetuximab	1 st : Irinotecan + cetuximab 2 nd : Eribulin 3 rd : Gemcitabine	1 st : PR 2 nd : PD 3 rd : PD	3 1 1	Dead
22	Colorectal	EGFR and PIK3CA	Irinotecan + Panitumumab	Irinotecan + Panitumumab	PR	2+	On treatment

20 patients received a personalized treatment and 6 achieved partial remissions and 7 were on treatment with at least disease stabilization.

Integrated Genomics and “Avatar” Mouse Models for Personalized Treatment of Pancreatic Cancer

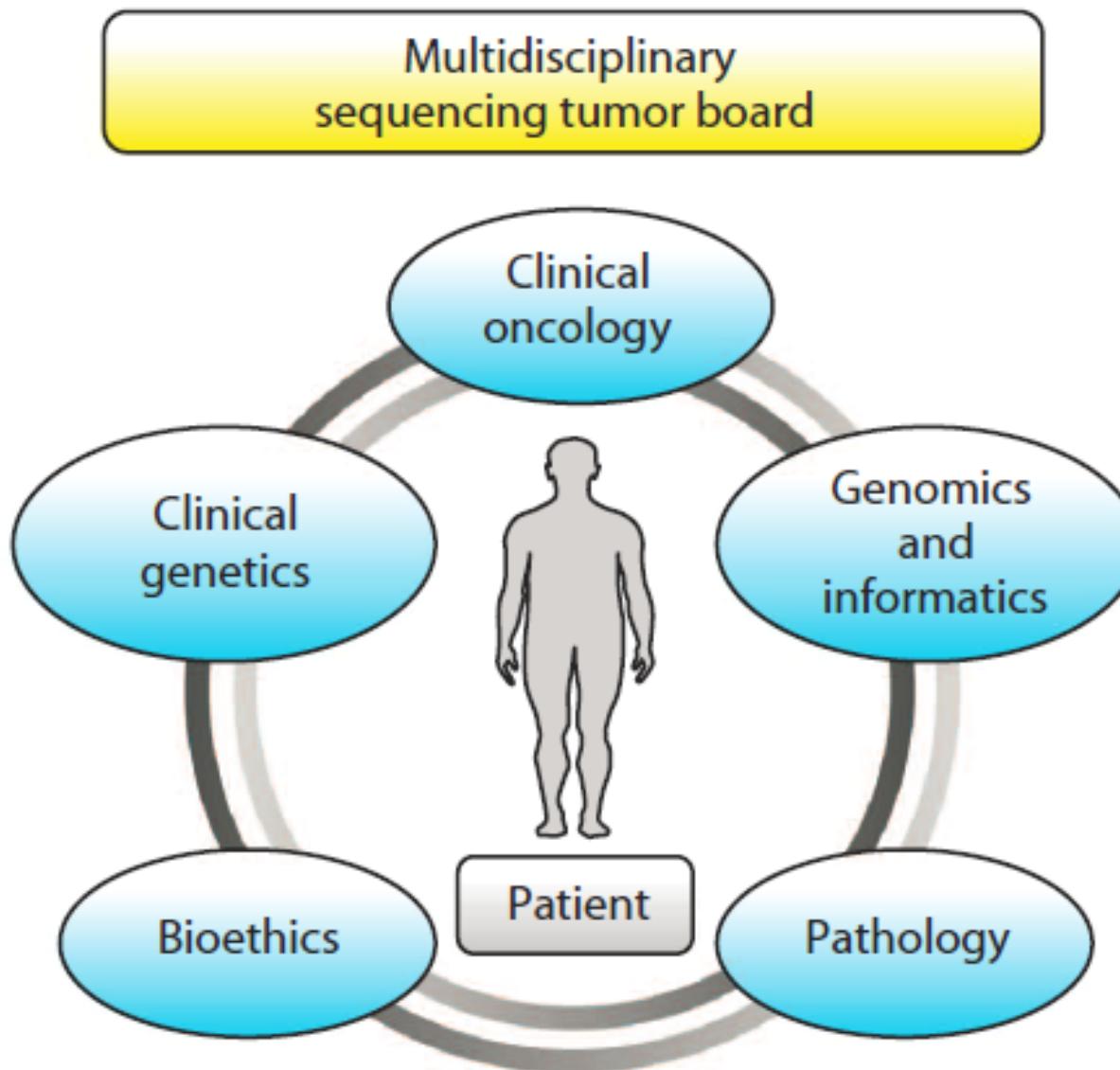
“We propose an **open label, multicenter, randomized research project** in patients with standard of care resistant metastatic pancreatic cancer aiming to test the hypothesis that **an integrated personalized treatment approach improves survival** compared to the conventional “one size fits all” treatment strategy.”

Patient Code	Branch	Sex	Age	Xenograft Code
Avatar-01	Conventional	M	76	
Avatar-02	Experimental	M	76	Panc-079
Avatar-03	Experimental	F	43	Panc-078
Avatar-04	Conventional	F	44	
Avatar-05	Conventional	F	71	
Avatar-06	Experimental	M	49	Panc-080
Avatar-07	Experimental	F	49	Panc-081
Avatar-08	Experimental	M	55	Panc-082
Avatar-09	Experimental	F	63	Panc-083
Avatar-10	Experimental	F	59	Panc-084



The diagram illustrates the personalized treatment process. A 'Personalized drug' is applied to an 'Avatar mouse' which is labeled as 'SENSITIVE' or 'RESISTANT'. The drug response is then used to identify 'Potential drugs based on Genomic profiling'.

Multidisciplinary Team



The Future

Here's my
sequence ...



Source: New Yorker

Genomic (Personalized) Medicine