Genomics in the Clinical Practice - Today and Tomorrow

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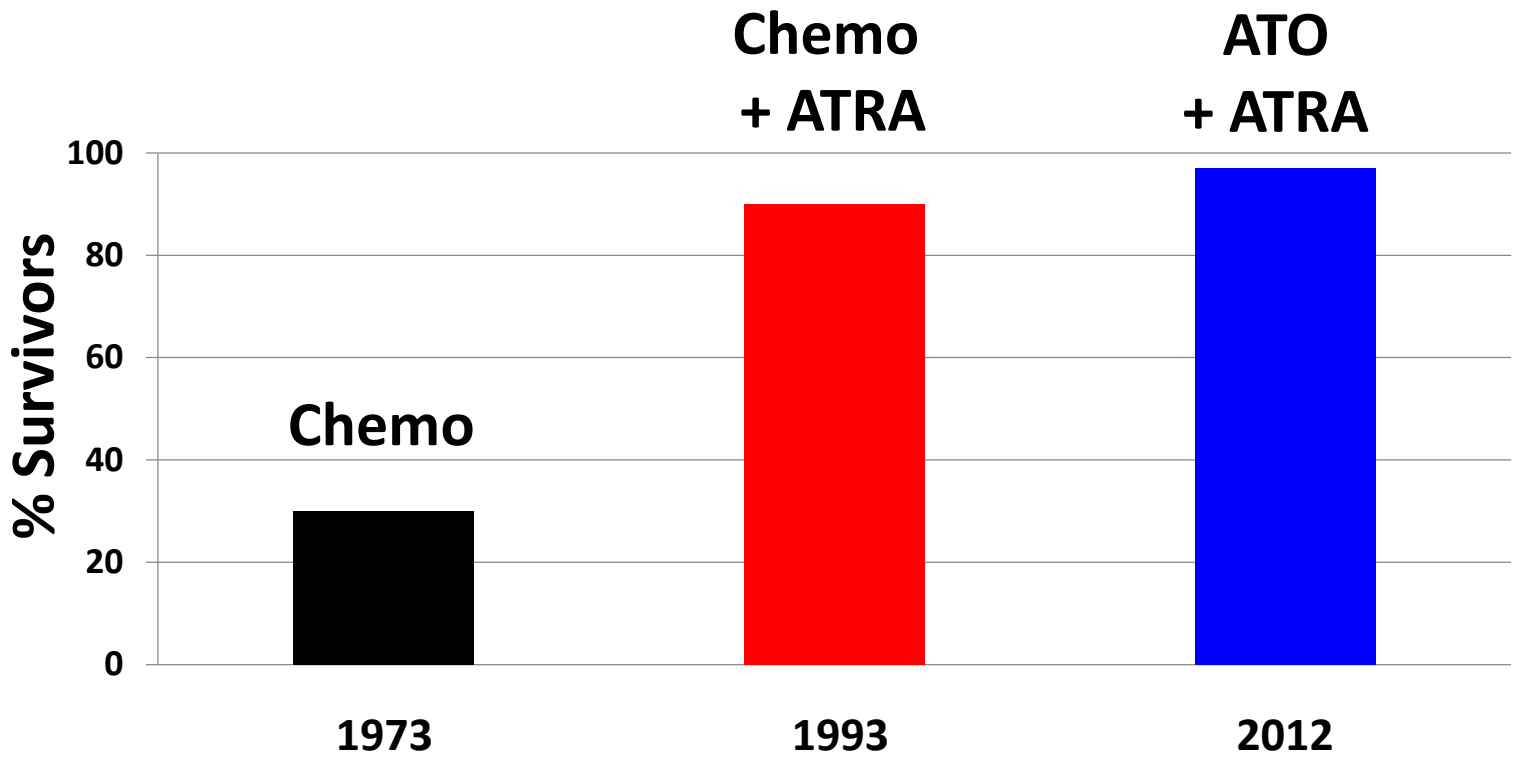
Workshop on Processing of Genomic Information: From Standards to Deployment

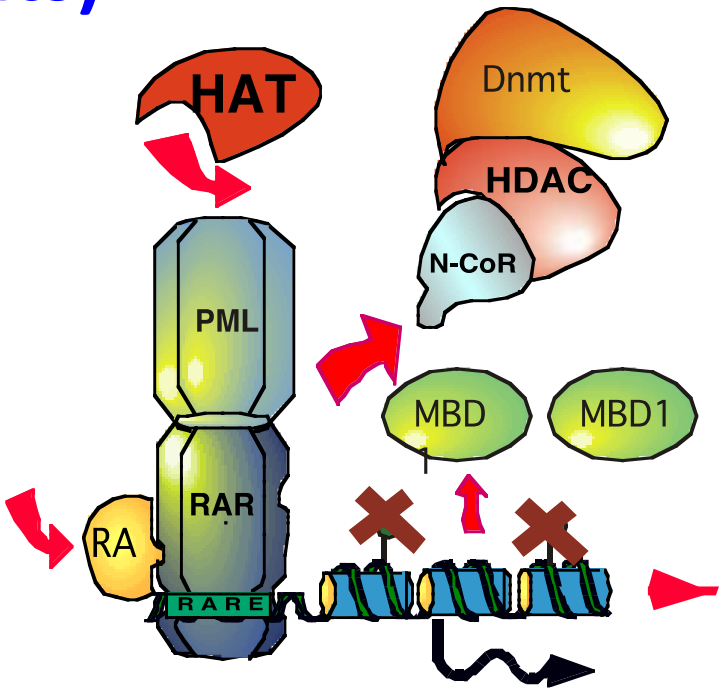
Turin, July 19th 2017

Precision/Personalized Medicine in Oncology: toward curative treatments (mechanism-based treatments)

1. The first example: Promyelocytic Leukemias



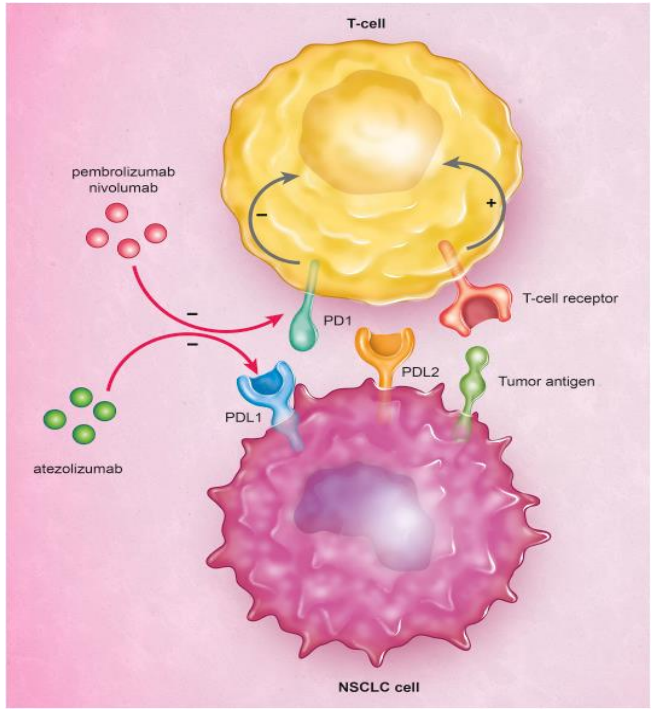
No therapy-related toxicity

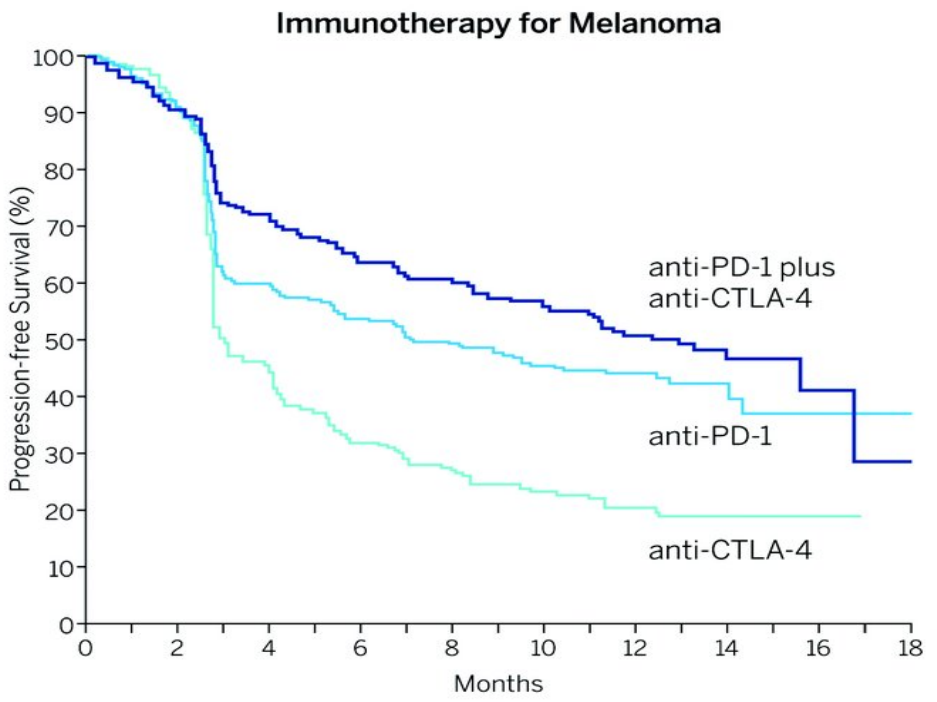


- Targeting of tumor-associated mutation
- Combination of Molecular Drugs
- Chemotherapy-free cure

Precision/Personalized Medicine in Oncology: toward curative treatments (mechanism-based treatments)

1. The last example: Cancer Immunotherapy with checkpoint inhibitors





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- **Targeting the micro-environment**
- **Prolonged remissions In metastatic melanomas**

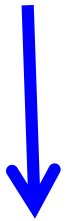
Other Molecular Drugs and other Success-Stories

Imatinib mesylate	CML	BCR-ABL translocation	Oncogene addiction (1982)
Imatinib mesylate Sunitinib Nilotinib Dasatinib	GIST Dermatofibrosarcoma protuberans Hypereosinophylic syndrome Melanoma	c-KIT mutation PDGFR mutation	Oncogene addiction (1999)
Trastuzumab Pertuzumab Lapatinib	Breast	HER2 amplification	Oncogene addiction (1985)
Gefitinib, Erlotanib Cetuxumab	Lung cancer Bowel	EGFR mutation	Oncogene addiction (2004)
PKC412, SU11248, CMT53518	AML, ALL	FLT-3 mutation, tandem duplication	Oncogene addiction (1996)
PARP inhibitors	Breast Ovarian	BRCA1/2 mutation	Synthetic lethality (2005)
PLX4032	Melanoma	BRAF (8 years)	Oncogene addiction (2002)
Crizotinib	Lung	EML-4 ALK (4 years)	Oncogene addiction (2007)
PCI 32765	CLL	BTK expression	Lineage (1993)
Tamoxifen, AIs	Breast cancer	ER expression	Lineage (1800s)

Molecular drugs have changed the natural history of different types of cancer

Central to Precision Medicine in Oncology is the identification of biomarkers

Identify
the PML-RAR mutation



Start
ATRA+ATO treatment

ATRA only works in leukemia patients that Carry PML-RAR mutations

In Italy: ~1,000 of the total ~10,000 myeloid-leukemia patients in 2013

Identify
the ALK mutation

Start
Cryzotinib treatment

Crizotinib only works in lung cancer patients that carry ALK mutations

In Italy: ~1,800 of the total ~60,000 lung cancer patients in 2013

Stratification for immunotherapy: 7 parameters of the immunogram

- Tumor foreigness
  - Neoantigens
  - Mutational load (a surrogate for neoantigens)
    - Melanoma
    - NSCLC
    - MSI colorectal
- Immune status (circulating immune cells)
  - Low lymphocytes
  - High neutrophils
  - High eosinophils
  - Myeloid-derived suppressive cells
- Immune cell infiltration
  - Type and amount of lymphocyte infiltration
- Immune checkpoint expression
  - PD-L1
  - IFNg
- Soluble inhibitors
  - IL1, IL6, IL17, CXCL1, PGE2
- Inhibitory tumor metabolism
  - LDH levels
  - Intratumoral glucose
  - Intratumoral hypoxia
- Tumor sensitivity to immune effectors
  - HLA levels/sequence

Blue: Can be studied by *DNA sequencing*

Red: can be studied by *RNA expression*

Strategy: combine

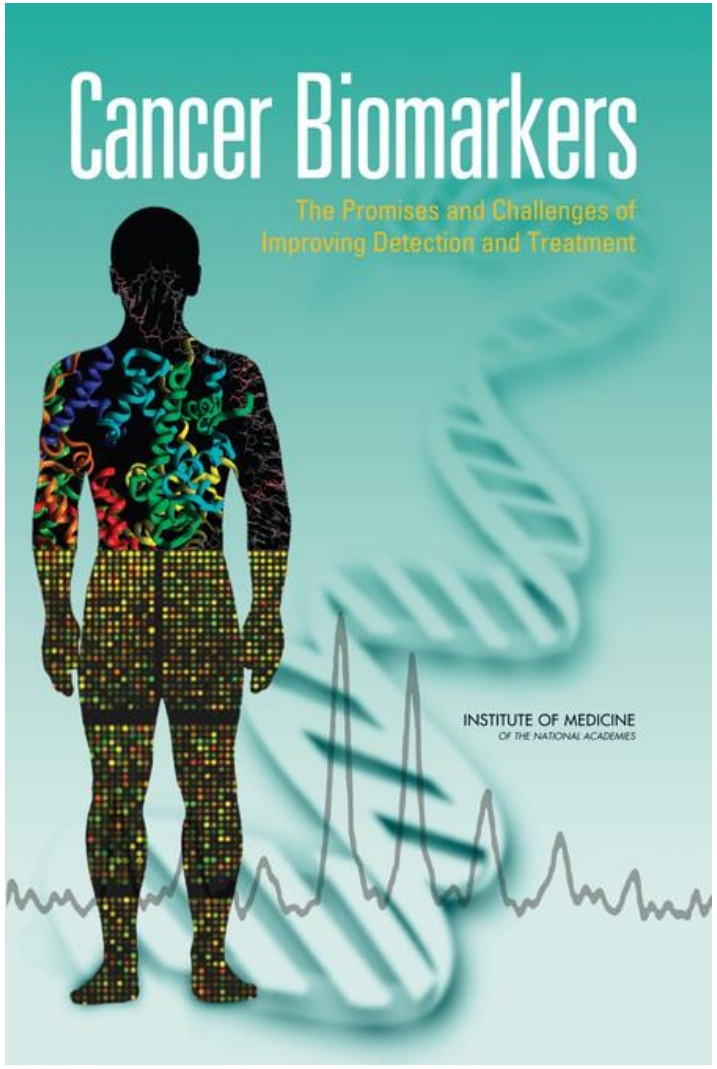
- gDNA seq (wes/wgs/panels)
- HLA typing
- TCR typing
- RNAseq/nanostring

Central to Precision Medicine in Oncology is the identification of biomarkers

- **The most effective targeted drugs are linked to response-prediction biomarkers**
  - Numbers of available drugs with associated stratification biomarkers is quickly expanding

- **Applications**
  - treatment selection
  - early detection
  - monitoring of treatment outcome
  - prediction of disease risk

- **Genomic markers have the greatest impact**
  - NGS: Rapidly evolving, relatively low cost
  - NGS of genomic alterations in thousands of tumors
  - Clinical application for cancer-patient stratifications
  - Leads the transition to omics-scale diagnostics



The challenges (limits) of Genomics and Precision Medicine

1. How to extend the benefits of currently available targeted treatments to all patients

- **low number of eligible patients accessing available targeted treatments (<20% in Italy?)**
  - **omic approaches are not standardized for clinical use**
  - **resources required are currently unsustainable in a routine clinical setting, in terms of costs, time and human effort**
  - **limited screening capabilities, drug availability, and training of practitioners**

➢ ***Guarantee access of patients to genomic screenings and to available targeting drugs***

The challenges (limits) of Genomics and Precision Medicine

2. How to increase the numbers of patients that can be cured with Precision Medicine Medicine approaches

- **Low number of tumors for which approved targeted treatments are available (<20%)**
- **Many drugs in clinical development**

➢ ***Guarantee access of patients to drug pipelines (Clinical Trials)***

The challenges (limits) of Genomics and Precision Medicine

3. How to increase efficacy of targeted treatments (curative treatments)

- **Most not curative; Short responses; Resistance dominant over sensitivity**
- **Poor value of available stratification markers**

➢ ***Urgent need: renewed effort in fundamental-research in oncology***

- **New approaches in Cancer Science (mechanisms of resistance; Tumor heterogeneity; single-cell omics; (micro)environmental interactions)**
- **New treatment approaches, new drugs and stratification markers**

The challenges (limits) of Genomics and Precision Medicine

4. How to identify new cancer-predisposing genes, environmental carcinogens and gene-environment interactions

- The type of genetic screening used to date (linkage or candidate-gene analyses, GWAS) h identified only a portion of the genetic risk factors (rare high-penetrance genes and common low-penetrance variants)
- Most of the genetic risk has yet to be discovered (large number of low-frequency moderate-penetrance genes)

- ***Genomic screenings in large and well characterized cohorts***
- ***Relationships between genes, diet, lifestyle, and environmental factors (population (epi)genomics)***

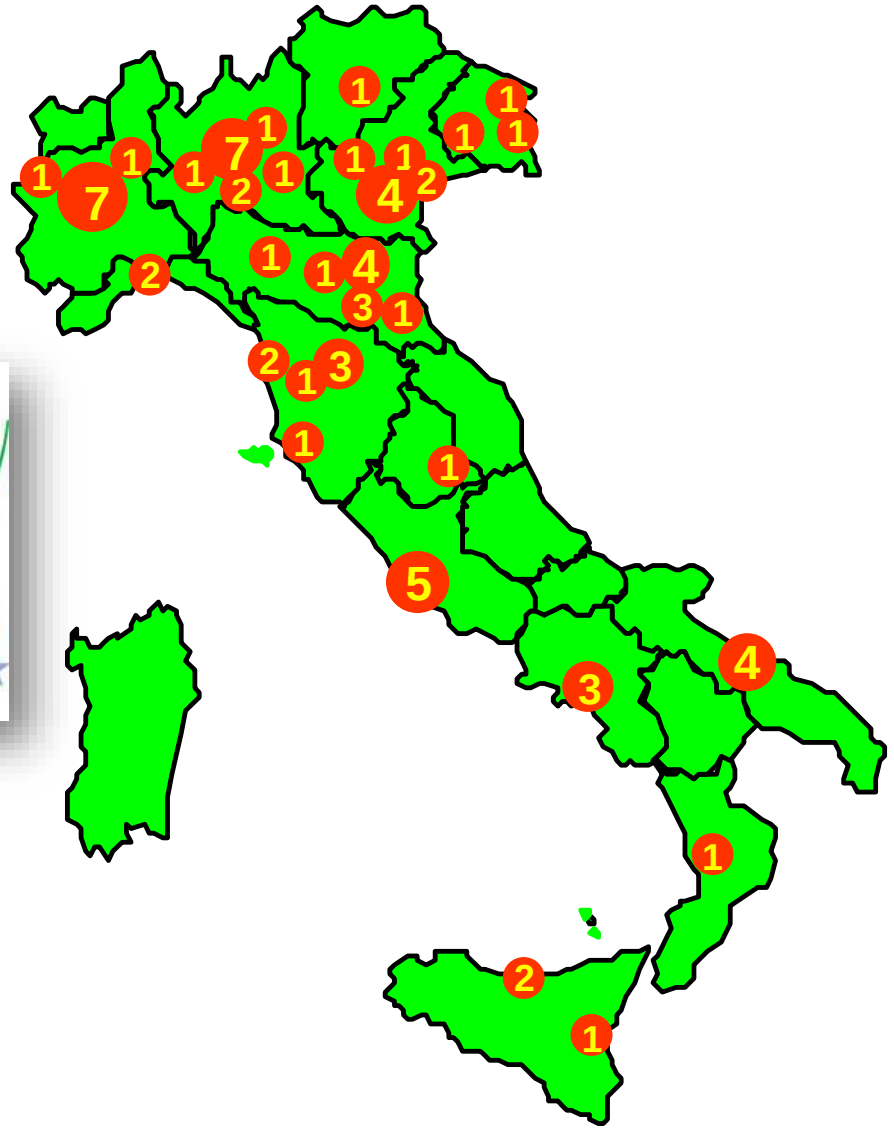
The challenges (limits) of Genomics and Precision Medicine

5. How to deal with the increasing difficulty in the collection and integration of a huge amount of "personalized data" (-omics, environmental, lifestyle, medical data, etc.)

- **Each patient requires collection and integration of a huge amount of "personalized data" (genomic, epigenomic, environmental, lifestyle and medical history)**
- **"personalized data" needs to be integrated with knowledge from both clinic and basic research**
- **the scale of emerging information is enormous and outpacing our human cognitive capacity**

➢ ***Generation of Large-scale Genomic and Clinical Data Resources (Prescription and Analytical Computational Tools)***

Alleanza Contro il Cancro (ACC)
21 IRCCS – Ministry of Health (+~50 affiliated Hospitals)



The 21 ACC IRCCS Research Hospitals:

Clinical Resources (2014)

- 90k New cancer patients every year
- 70k Patients in Clinical Trials
- 5k Active Clinical Trials

Research performance (2016)

- Number of publications: > 5,000
- Impact Factor: > 20,000
- Research Grants: >200,000,000
- High-Impact Journals

Collaboration with Patients' Associations

Collaboration with the Ministry of Health for NHS regulations

The ACC Precision-Medicine Program

- **Promotion of national programs of genomic-screenings and genomics-based clinical trials**

- **Dissemination of Genomics-capabilities (e.g. set-up of NGS-facilities at each IRCCS; training of a new generation of genomics technologists and clinical bioinformaticians)**

- **Set-up of the ACC IT-infrastructure (in coll. with Elixir): Generation of prescription and analytical computational tools, and of a national database of cancer mutations**

What to sequence

- Gene Panels of Actionable genes (for tumors with know mutations)
  - Nation-wide screens
  - ~200-330 Euros

- WGS/WES for “genomically uncharacterized” tumors
  - Retrospective analyses on selected tumor populations
  - Ret~1,000-2,500 Euros

The first National Genomic Screening in Oncology (ACC Lung-cancer screening; Sept. 2017)

1. Genomic profile of every patient (tumor+germline)

→

- Identification of actionable somatic mutations
- Identification of germline pharmacogenomic variants
- Identification of driver-gene mutations

- Treatment-stratification
- Drug-toxicity
- New stratification markers

↓

- Identification of germline cancer-risk variants

→

2. Mapping of each risk-variant In family members

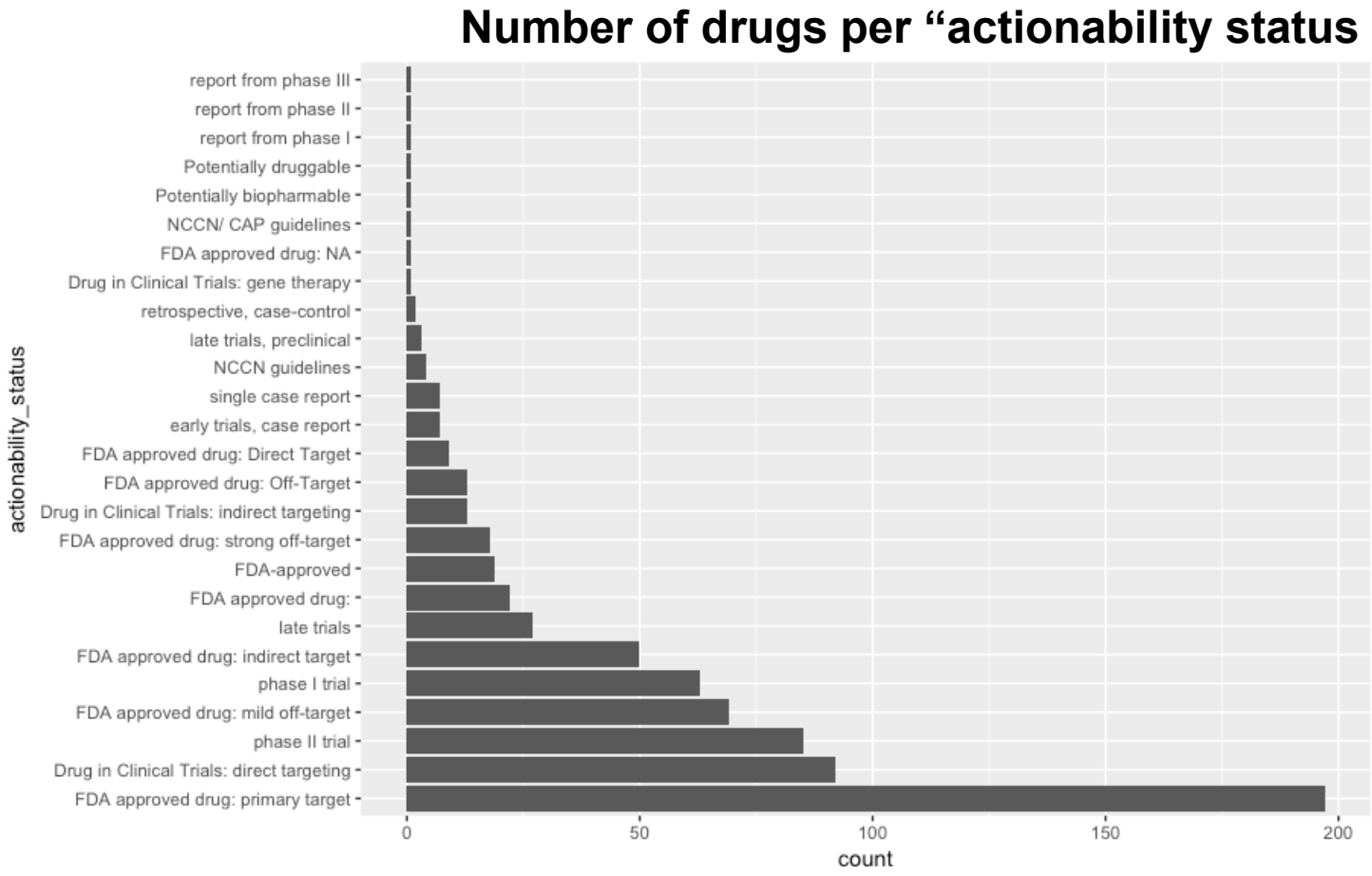
→

- Cancer-prevention plans

Clinical Value of the Somatic Actionable-Genome: Numbers of Drugs

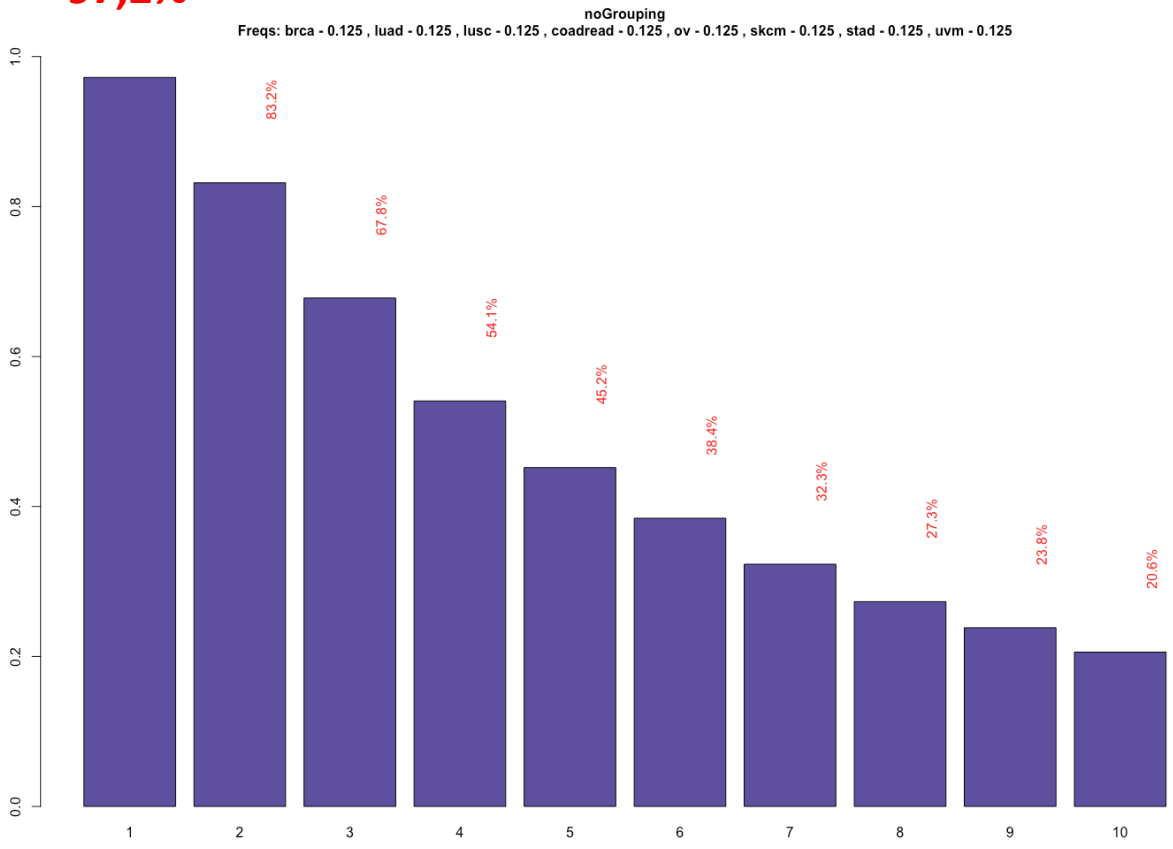
Genetic links to 485 Drugs:

- **57 with FDA-approved indications in oncology**
- **322 with other FDA approved indications**
- **106 Drugs in Clinical Trial**

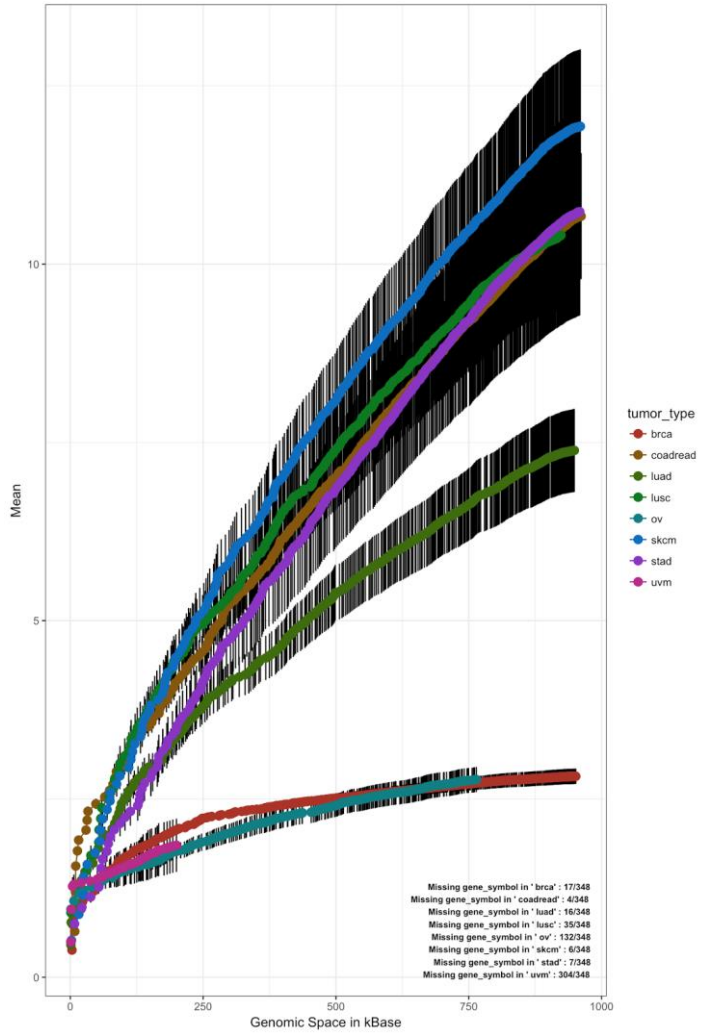


Detection Power of the Somatic Actionable Genome (Lung Cancer)

97,2%

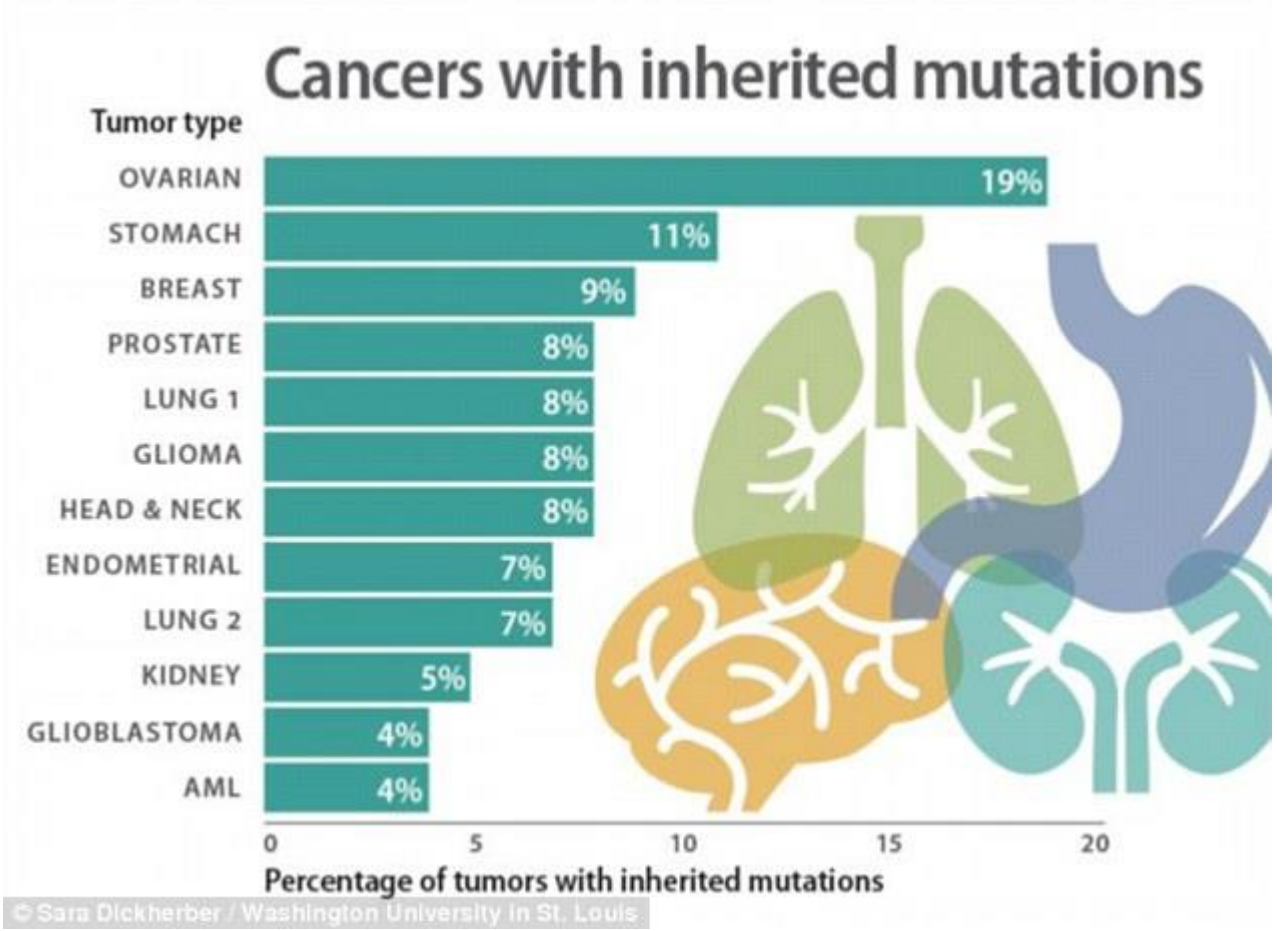


97% of patients with at least onel Actionable Mutation

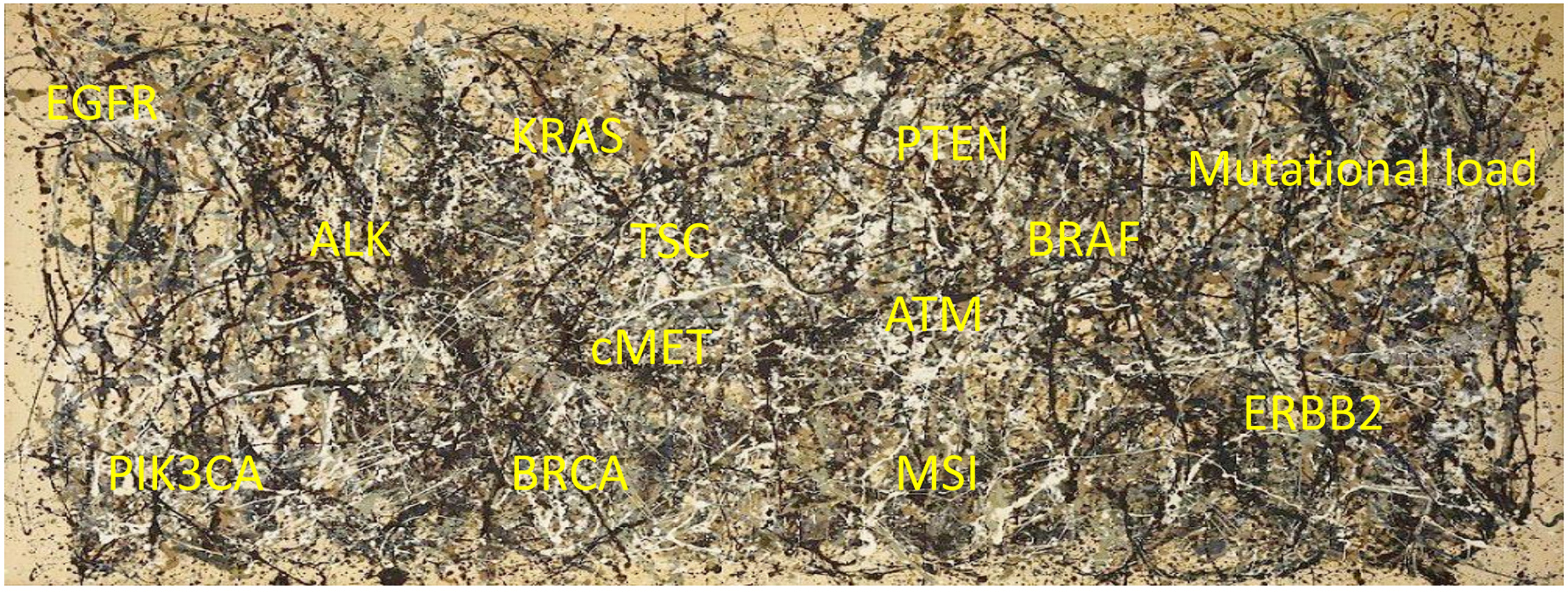


Average of 3-15 actionable mutations per patient

Clinical Value of the Germline Actionable-Genome (116 genes)

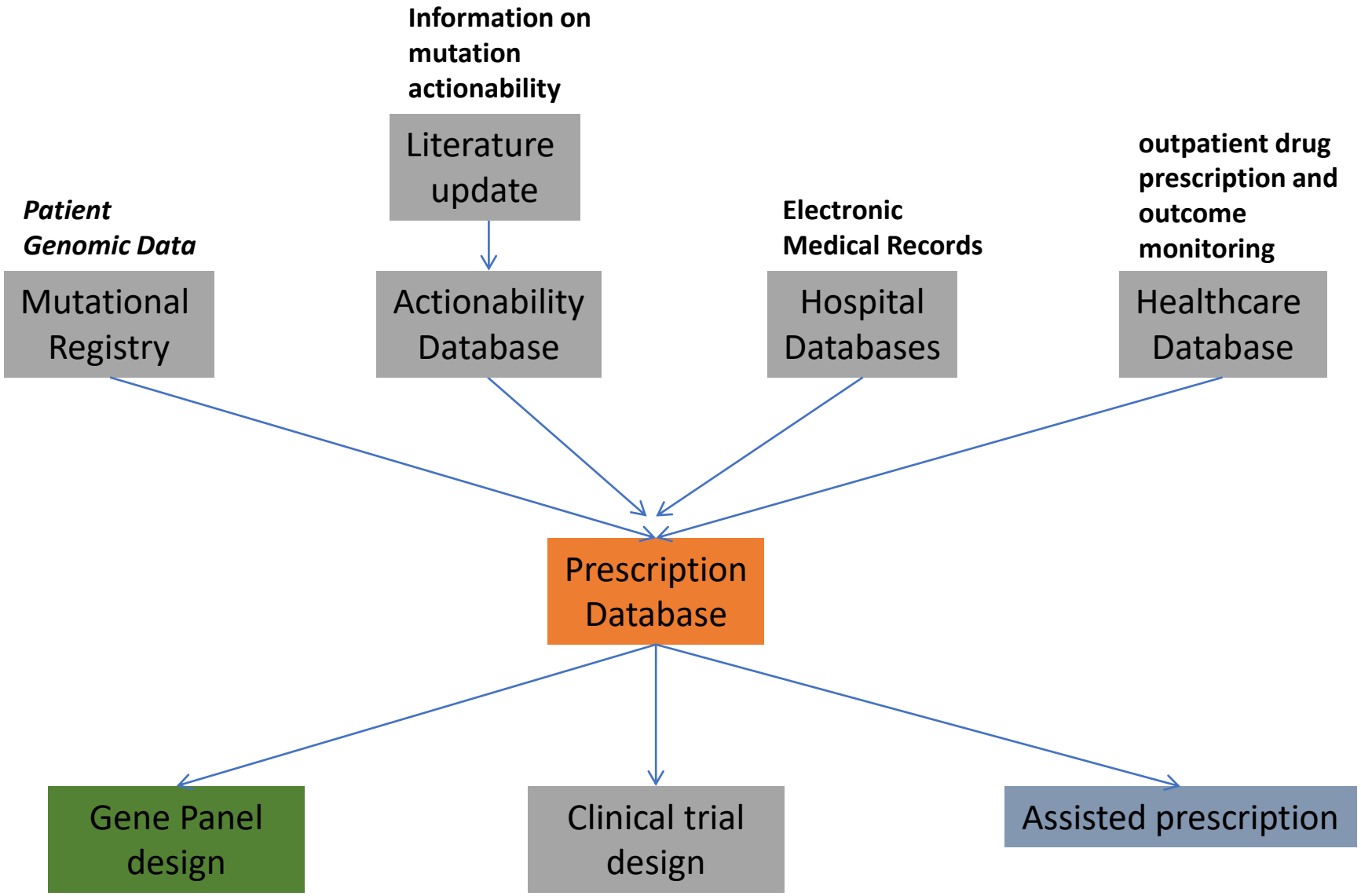


Clinical decision making in 2017

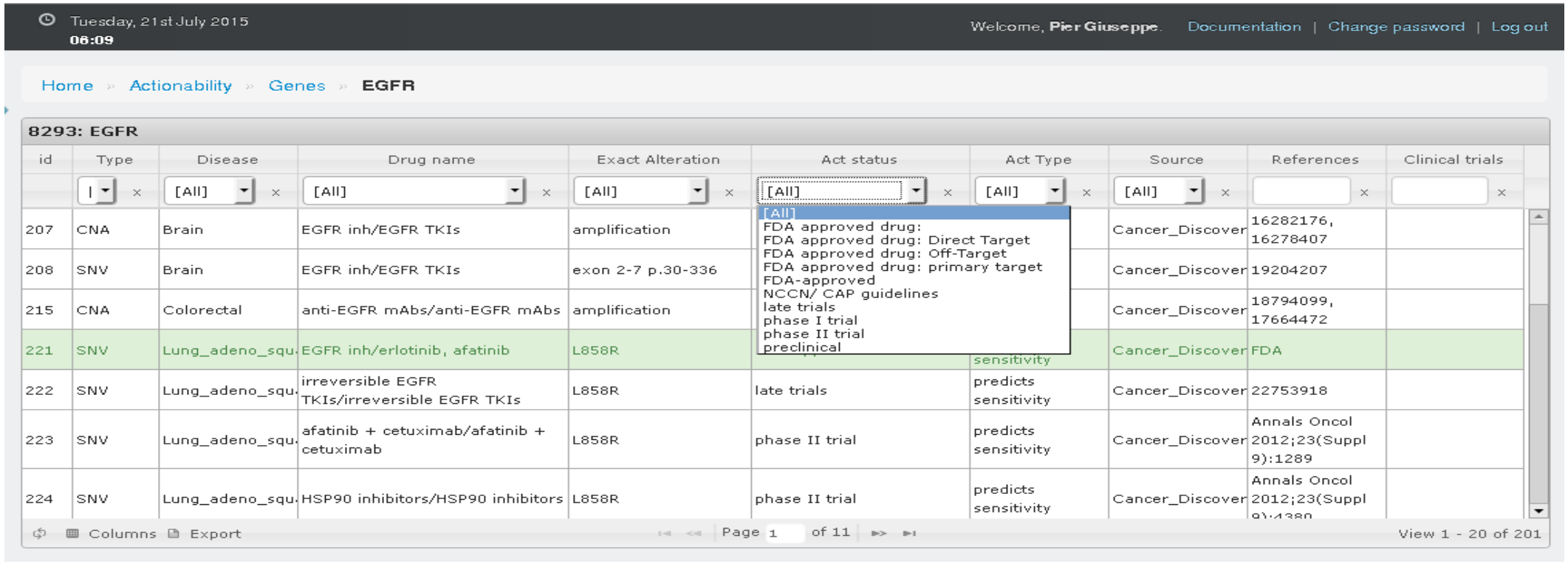


The ACC prescription database

(in coll with IEO, Bicocca Un. And Politecnico Milan)



THE ACC PRESCRIPTION DATABASE



id	Type	Disease	Drug name	Exact Alteration	Act status	Act Type	Source	References	Clinical trials
207	CNA	Brain	EGFR inh/EGFR TKIs	amplification			Cancer_Discover	16282176, 16278407	
208	SNV	Brain	EGFR inh/EGFR TKIs	exon 2-7 p.30-336			Cancer_Discover	19204207	
215	CNA	Colorectal	anti-EGFR mAbs/anti-EGFR mAbs	amplification			Cancer_Discover	18794099, 17664472	
221	SNV	Lung_adeno_squ	EGFR inh/erlotinib, afatinib	L858R		sensitivity	Cancer_Discover	FDA	
222	SNV	Lung_adeno_squ	irreversible EGFR TKIs/irreversible EGFR TKIs	L858R	late trials	predicts sensitivity	Cancer_Discover	22753918	
223	SNV	Lung_adeno_squ	afatinib + cetuximab/afatinib + cetuximab	L858R	phase II trial	predicts sensitivity	Cancer_Discover	Annals Oncol 2012;23(Suppl 9):1289	
224	SNV	Lung_adeno_squ	HSP90 inhibitors/HSP90 inhibitors	L858R	phase II trial	predicts sensitivity	Cancer_Discover	Annals Oncol 2012;23(Suppl	

Id: entry id
Type: type of mutation (SNV, CAN, germline, translocation or other)
Disease: the disease for which that relationship is observed
Drug name: merges drug category/drug name
Exact alteration: site of mutation if SNV, amp o del se CAN, translocation partner se translocation
Act status: the contest in which the relationship is observed
Act type: predicts sensitivity or resistance, prognostic (nothing else)
Source: one of the four original databases (Cancer Discovery, Mills, Target (Broad), Intogen) or ACC
References: Pubmed ID of the supporting paper
Clinical trials: clinical trials.gov ID of available trials (in development)

DICTIONARY MATCHING

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JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Primary and Secondary Kinase Genotypes Correlate With the Biological and Clinical Activity of Sunitinib in Imatinib-Resistant Gastrointestinal Stromal Tumor

Michael C. Heinrich, Robert G. Maki, Christopher L. Corless, Cristina R. Antonescu, Amy Harlow, Diana Griffith, Ajia Town, Arin McKinley, Wen-Bin Ou, Jonathan A. Fletcher, Christopher D.M. Fletcher, Xin Huang, Darrel P. Cohen, Charles M. Baum, and George D. Demetri

From the Oregon Health and Science University Cancer Institute and Portland Veterans Affairs Medical Center, Portland, OR; Memorial Sloan-Kettering Cancer Center, New York, NY; Dana-Farber Cancer Institute, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA; and Pfizer Global Research and Development, La Jolla, CA.

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Presented in part at the 41st Annual Meeting of the American Society of Clinical Oncology, May 13-17, 2005, Orlando, FL; the 13th European Cancer Conference, October 30-November 3, 2005, Paris, France; the 42nd Annual Meeting of the American Society of Clinical Oncology, June 2-6, 2006, Atlanta, GA; and the 1st American Association for Cancer Research Conference on Molecular Diagnostics in Cancer Therapeutic Development, September 12-15, 2006, Chicago, IL.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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A B S T R A C T

Purpose
Most gastrointestinal stromal tumors (GISTs) harbor mutant KIT or platelet-derived growth factor receptor α (PDGFRA) kinases, which are imatinib targets. Sunitinib, which targets KIT, PDGFRs, and several other kinases, has demonstrated efficacy in patients with GIST after they experience imatinib failure. We evaluated the impact of primary and secondary kinase genotype on sunitinib activity.

Patients and Methods
Tumor responses were assessed radiologically in a phase I/II trial of sunitinib in 97 patients with metastatic, imatinib-resistant/intolerant GIST. *KIT/PDGFRA* mutational status was determined for 78 patients by using tumor specimens obtained before and after prior imatinib therapy. Kinase mutants were biochemically profiled for sunitinib and imatinib sensitivity.

Results
Clinical benefit (partial response or stable disease for ≥ 6 months) with sunitinib was observed for the three most common primary GIST genotypes: *KIT* exon 9 (58%), *KIT* exon 11 (34%), and wild-type *KIT/PDGFRA* (56%). Progression-free survival (PFS) was significantly longer for patients with primary *KIT* exon 9 mutations ($P = .0005$) or with a wild-type genotype ($P = .0356$) than for those with *KIT* exon 11 mutations. The same pattern was observed for overall survival (OS). PFS and OS were longer for patients with secondary *KIT* exon 13 or 14 mutations (which involve the KIT-adenosine triphosphate binding pocket) than for those with exon 17 or 18 mutations (which involve the KIT activation loop). Biochemical profiling studies confirmed the clinical results.

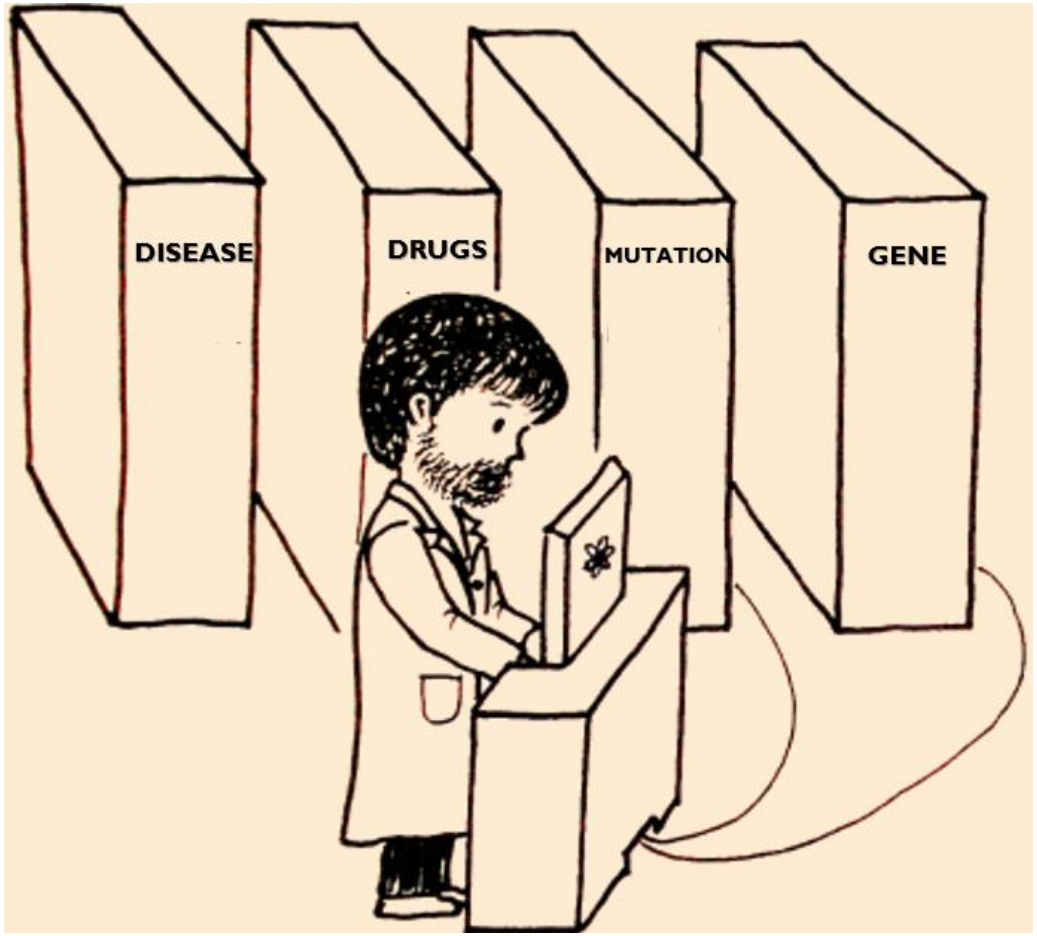
Conclusion
The clinical activity of sunitinib after imatinib failure is significantly influenced by both primary and secondary mutations in the predominant pathogenic kinases, which has implications for optimization of the treatment of patients with GIST.

J Clin Oncol 26:5352-5359. © 2008 by American Society of Clinical Oncology

INTRODUCTION

The pathogenesis of most gastrointestinal stromal tumors (GISTs) results from activating mutations of KIT or of platelet-derived growth factor receptor α (PDGFRA). More than 80% of GISTs express mutated, constitutively active KIT, and another 5% to 7% express mutated PDGFRA; 10% to 15% of tumors have no associated mutations in these kinases.[1-3]

Imatinib mesylate, a selective inhibitor of KIT and PDGFRA (and of platelet-derived growth factor receptor β [PDGFRB] and BCR-ABL kinase), has revolutionized the treatment of GIST; however, up to 14% of GISTs exhibit primary resistance to imatinib (defined as progression within 3 to 6 months of initiating therapy),[4-6] and another 40% to 50% develop resistance within 2 years of beginning therapy (ie, secondary resistance).[5,6] Sunitinib malate (SUTENT; Pfizer, New York, NY), another small-molecule tyrosine kinase inhibitor (TKI) with selectivity for KIT and PDGFRA (and for PDGFRB, all three isoforms of vascular endothelial growth factor receptor [VEGFR], FMS-like tyrosine kinase 3 [FLT3], colony-stimulating factor 1 receptor [CSF-1R], and glial cell line-derived neurotrophic factor receptor [rearranged during transfection; RET; Pfizer, New York, NY; data on file]),[7-11] has demonstrated clinical benefit in phase I to phase III



DRUGS FDA

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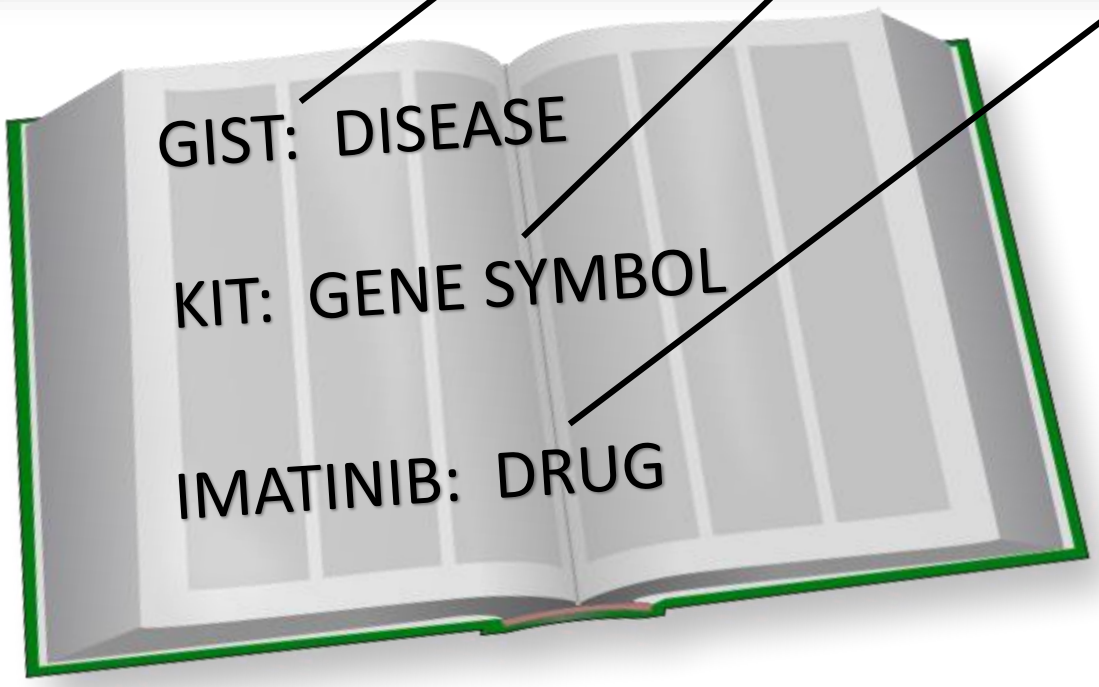
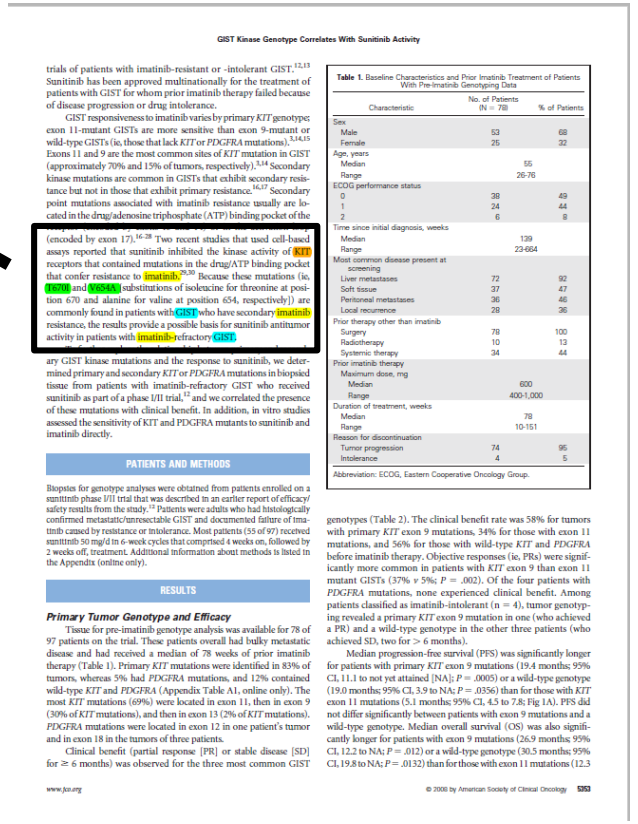
(encoded by exon 17).[16-28] Two recent studies that used cell-based assays reported that sunitinib inhibited the kinase activity of KIT receptors that contained mutations in the drug/ATP binding pocket that confer resistance to imatinib.[29,30] Because these mutations (ie, T670I and V654A [substitutions of isoleucine for threonine at position 670 and alanine for valine at position 654, respectively]) are commonly found in patients with GIST who have secondary imatinib resistance, the results provide a possible basis for sunitinib antitumor activity in patients with imatinib-refractory GIST.





GIST Kinase Genotype Correlates With Sunitinib Activity

trials of patients with imatinib-resistant or -intolerant GIST.[12,13] Sunitinib has been approved multinationally for the treatment of patients with GIST for whom prior imatinib therapy failed because of disease progression or drug intolerance.

GIST responsiveness to imatinib varies by primary *KIT* genotype; exon 11-mutant GISTs are more sensitive than exon 9-mutant or wild-type GISTs (ie, those that lack *KIT* or *PDGFRA* mutations).[3,14,15] Exons 11 and 9 are the most common sites of *KIT* mutation in GIST (approximately 70% and 15% of tumors, respectively).[3,14] Secondary kinase mutations are common in GISTs that exhibit secondary resistance but not in those that exhibit primary resistance.[16,17] Secondary point mutations associated with imatinib resistance usually are located in the drug/adenosine triphosphate (ATP) binding pocket of the

(encoded by exon 17).[16-28] Two recent studies that used cell-based assays reported that sunitinib inhibited the kinase activity of KIT receptors that contained mutations in the drug/ATP binding pocket that confer resistance to imatinib.[29,30] Because these mutations (ie, T670I and V654A [substitutions of isoleucine for threonine at position 670 and alanine for valine at position 654, respectively]) are commonly found in patients with GIST who have secondary imatinib resistance, the results provide a possible basis for sunitinib antitumor activity in patients with imatinib-refractory GIST.

ary GIST kinase mutations and the response to sunitinib, we determined primary and secondary *KIT* or *PDGFRA* mutations in biopsied tissue from patients with imatinib-refractory GIST who received sunitinib as part of a phase I/II trial,[12] and we correlated the presence of these mutations with clinical benefit. In addition, in vitro studies assessed the sensitivity of KIT and PDGFRA mutants to sunitinib and imatinib directly.

Table 1. Baseline Characteristics and Prior Imatinib Treatment of Patients With Pre-Imatinib Genotyping Data

Characteristic	No. of Patients (N = 78)	% of Patients
Sex		
Male	53	68
Female	25	32
Age, years		
Median	55	
Range	26-76	
ECOG performance status		
0	38	49
1	24	44
2	6	8
Time since initial diagnosis, weeks		
Median	139	
Range	23-664	
Most common disease present at screening		
Liver metastases	72	92
Soft tissue	37	47
Peritoneal metastases	36	46
Local recurrence	28	36
Prior therapy other than imatinib		
Surgery	78	100
Radiotherapy	10	13
Systemic therapy	34	44
Prior imatinib therapy		
Maximum dose, mg		
Median	600	
Range	400-1,000	
Duration of treatment, weeks		
Median	78	
Range	10-151	
Reason for discontinuation		
Tumor progression	74	95
Intolerance	4	5

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

PATIENTS AND METHODS

Biopsies for genotype analyses were obtained from patients enrolled on a sunitinib phase I/II trial that was described in an earlier report of efficacy/safety results from the study.[12] Patients were adults who had histologically confirmed metastatic/unresectable GIST and documented failure of imatinib caused by resistance or intolerance. Most patients (55 of 97) received sunitinib 50 mg/d in 6-week cycles that comprised 4 weeks on, followed by 2 weeks off, treatment. Additional information about methods is listed in the Appendix (online only).

RESULTS

Primary Tumor Genotype and Efficacy

Tissue for pre-imatinib genotype analysis was available for 78 of 97 patients on the trial. These patients overall had bulky metastatic disease and had received a median of 78 weeks of prior imatinib therapy (Table 1). Primary *KIT* mutations were identified in 83% of tumors, whereas 5% had *PDGFRA* mutations, and 12% contained wild-type *KIT* and *PDGFRA* (Appendix Table A1, online only). The most *KIT* mutations (69%) were located in exon 11, then in exon 9 (30% of *KIT* mutations), and then in exon 13 (2% of *KIT* mutations). *PDGFRA* mutations were located in exon 12 in one patient's tumor and in exon 18 in the tumors of three patients.

Clinical benefit (partial response [PR] or stable disease [SD] for ≥ 6 months) was observed for the three most common GIST genotypes (Table 2). The clinical benefit rate was 58% for tumors with primary *KIT* exon 9 mutations, 34% for those with exon 11 mutations, and 56% for those with wild-type *KIT* and *PDGFRA* before imatinib therapy. Objective responses (ie, PRs) were significantly more common in patients with *KIT* exon 9 than exon 11 mutant GISTs (37% *v* 5%; $P = .002$). Of the four patients with *PDGFRA* mutations, none experienced clinical benefit. Among patients classified as imatinib-intolerant (n = 4), tumor genotyping revealed a primary *KIT* exon 9 mutation in one (who achieved a PR) and a wild-type genotype in the other three patients (who achieved SD, two for > 6 months).

Median progression-free survival (PFS) was significantly longer for patients with primary *KIT* exon 9 mutations (19.4 months; 95% CI, 11.1 to not yet attained [NA]; $P = .0005$) or a wild-type genotype (19.0 months; 95% CI, 3.9 to NA; $P = .0356$) than for those with *KIT* exon 11 mutations (5.1 months; 95% CI, 4.5 to 7.8; Fig 1A). PFS did not differ significantly between patients with exon 9 mutations and a wild-type genotype. Median overall survival (OS) was also significantly longer for patients with exon 9 mutations (26.9 months; 95% CI, 12.2 to NA; $P = .012$) or a wild-type genotype (30.5 months; 95% CI, 19.8 to NA; $P = .0132$) than for those with exon 11 mutations (12.3

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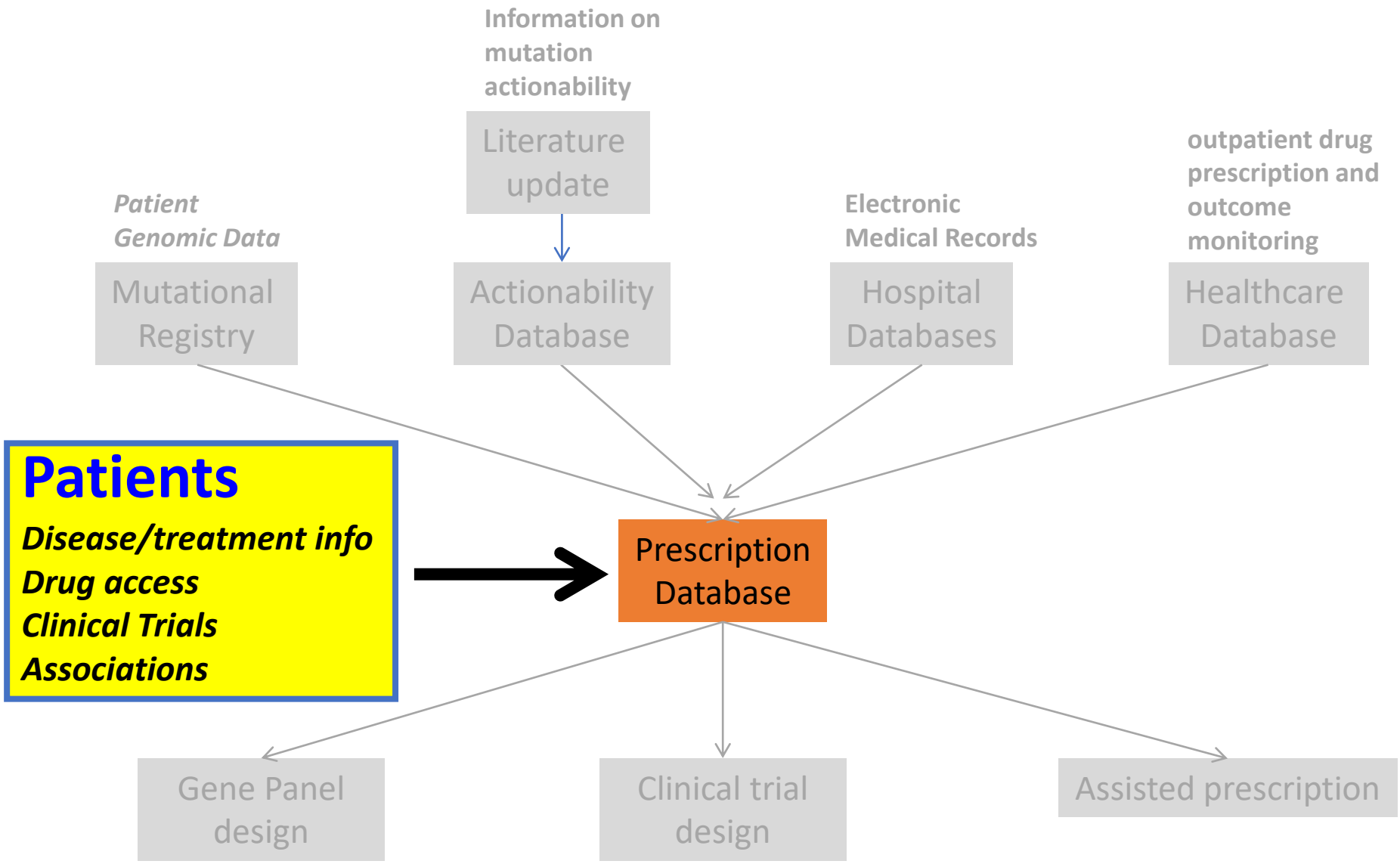
ENTITY EXTRACTION

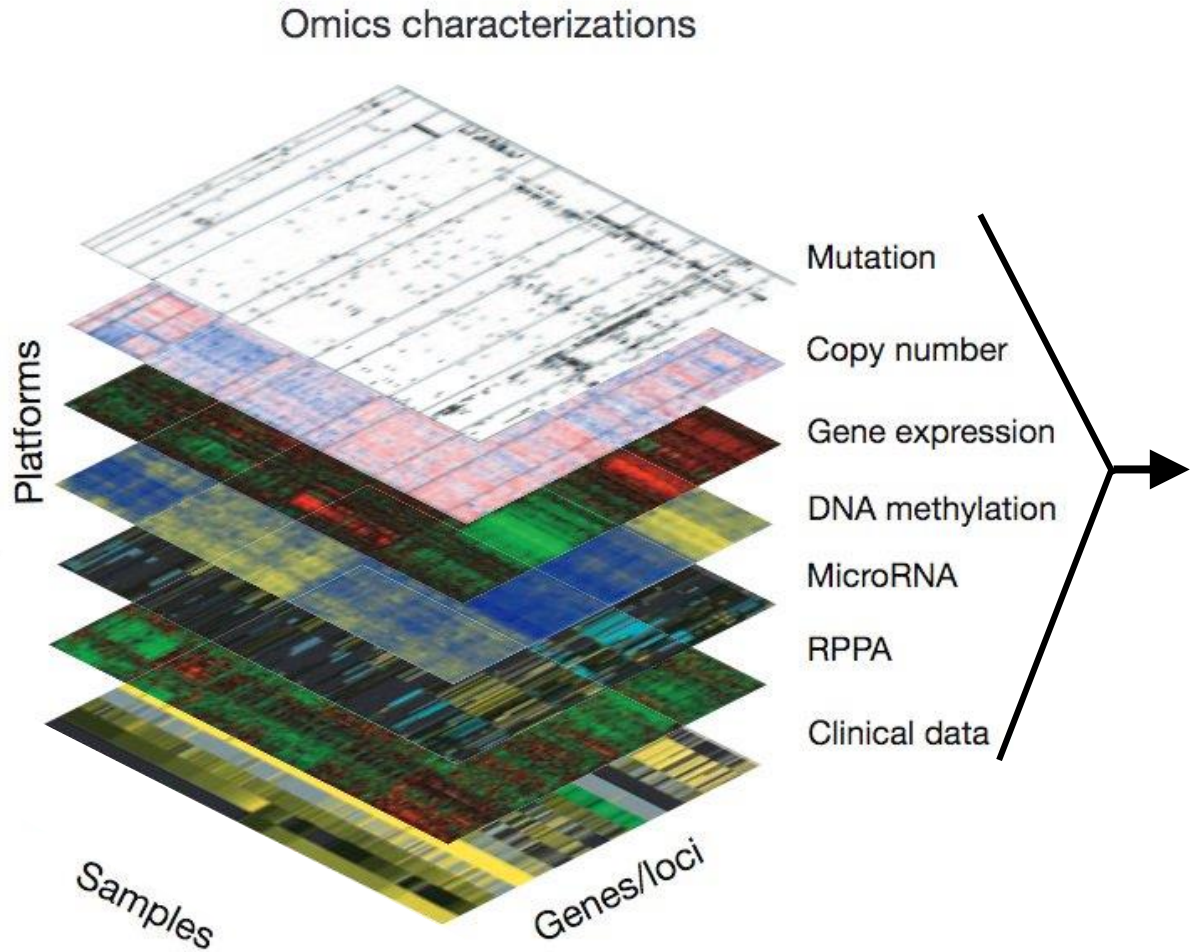
The ACC prescription database

(in coll with IEO, Bicocca Un. And Politecnico Milan)



Deciphering osteosarcoma omics to improve therapeutic targeting: A retrospective analysis of 400 patients

- **WGS**
- **WES**
- **RPPA**



Osteosarcoma is a major sarcoma type that is still poorly characterized and not object of study by large genome consortia.
400 osteosarcoma patients will be analyzed by multiple omics technologies in order to define all the druggable pathways to be tested in preclinical models and in clinical trials

ACC IT-infrastructure
(2017-2018; in coll, with Elixir, CNR, Cineca)

ACC core:

- LIMS
- Raw Data Storage
- HPC
- Bioinformatics pipelines

ACC Variant registry

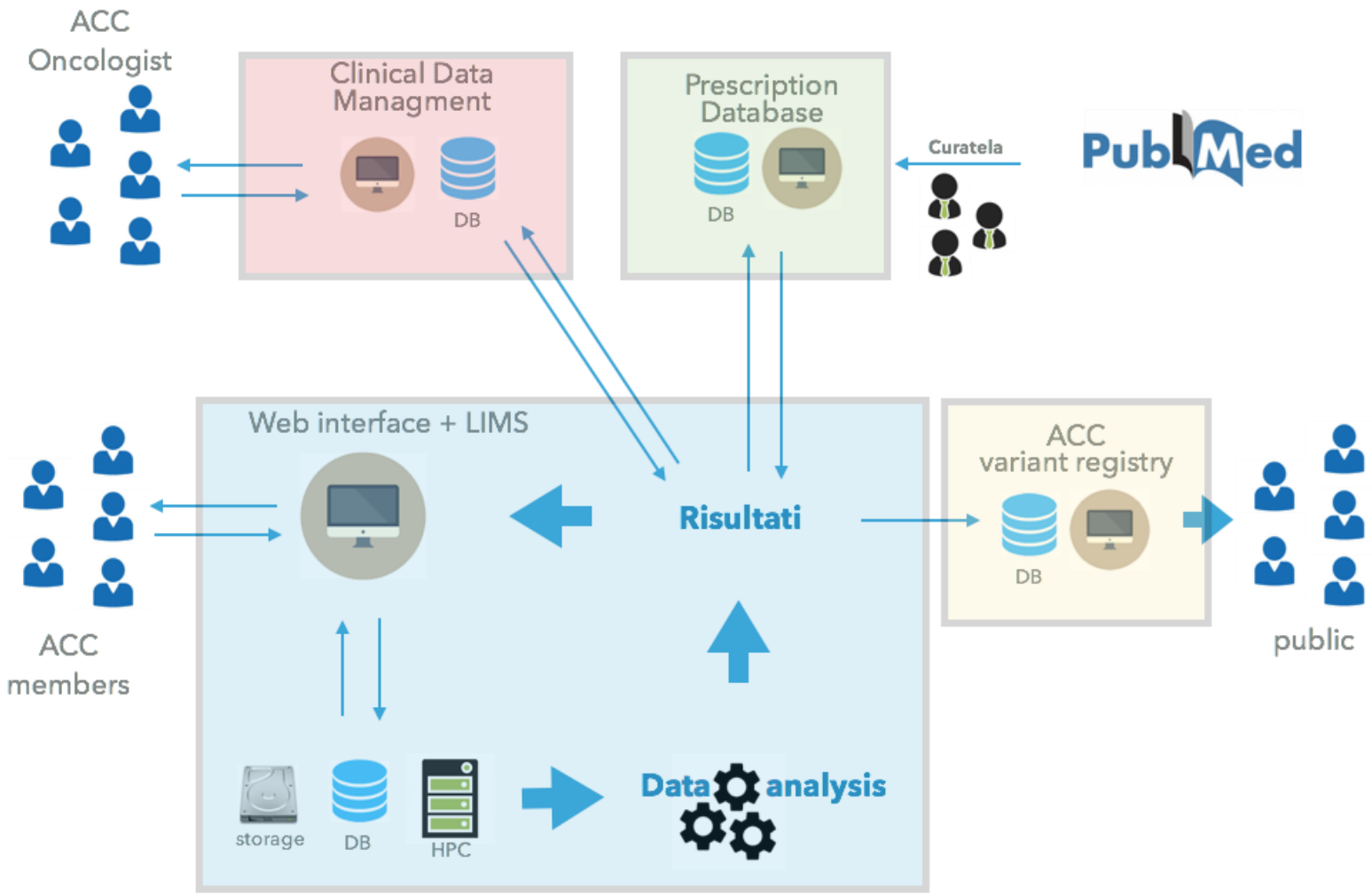
- Web interface
- Database
- Processed Data storage

ACC Prescription Database

- Data mining
- Web interface
- Database

ACC Clinical Data management

- Web interface; Database



ACC IT-infrastructure
(2017-2018; in coll, with Elixir, CNR, Cineca)

Sequencing projects 2018

ACC-Lung
- size targeted genome: 800 Kb
- 800 pazienti
- storage raw data: 2-10 Gb per sample
- 2 samples x patient
- **tot storage estimate: 3.2 Tb - 16 Tb**

Gersom
- size targeted genome: 3 Mb
- 1000 pazienti
- 2 samples x patient
- storage raw data: 8-40 Gb per sample
- **tot. storage estimated: 8 Tb - 40 Tb**

Immune Gene Panel
- size targeted genome**:** Unknown, estimated 800 kb
- 500 patients
- 2 samples x patient
- storage raw data: 2-10 Gb per sample
- **tot estimate: 2 Tb - 16 Tb**

Sarcoma
- Whole exam sequencing
- estimated 450 samples
- storage raw data: 20-60 Gb per sample
- 450 + 20 = **9 Tb - 16 Tb**

- RNA-seq sequencing
- estimated 450 samples
- storage raw data: **??** Gb per sample
- 450 + 20 = **9 Tb - 16 Tb**

- Targeted panel
- size: unknown, estimated 800 kb
- 500 patients
- 2 samples x patient
- storage raw data: 2-10 Gb per sample
- **tot estimate: 2 Tb - 16 Tb**

Tot storage estimated:
min: 31 Tb
max: 120 Tb