



The Best of the Year 2018

ROMA - 19 dicembre 2018
NH Collection Vittorio Veneto

DALLA MUTAZIONE ALLA
NETWORK ANALYSIS

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Potenziali Conflitti di Interesse

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Il Prof. Paolo Marchetti ha ricevuto, direttamente o attraverso Enti e/o Associazioni e/o Fondazioni a lui comunque riconducibili, compensi economici per la partecipazione a congressi, convegni, corsi o advisory board come pure fondi di ricerca, elargizioni liberali o contributi economici di qualsivoglia natura dalle seguenti Aziende:

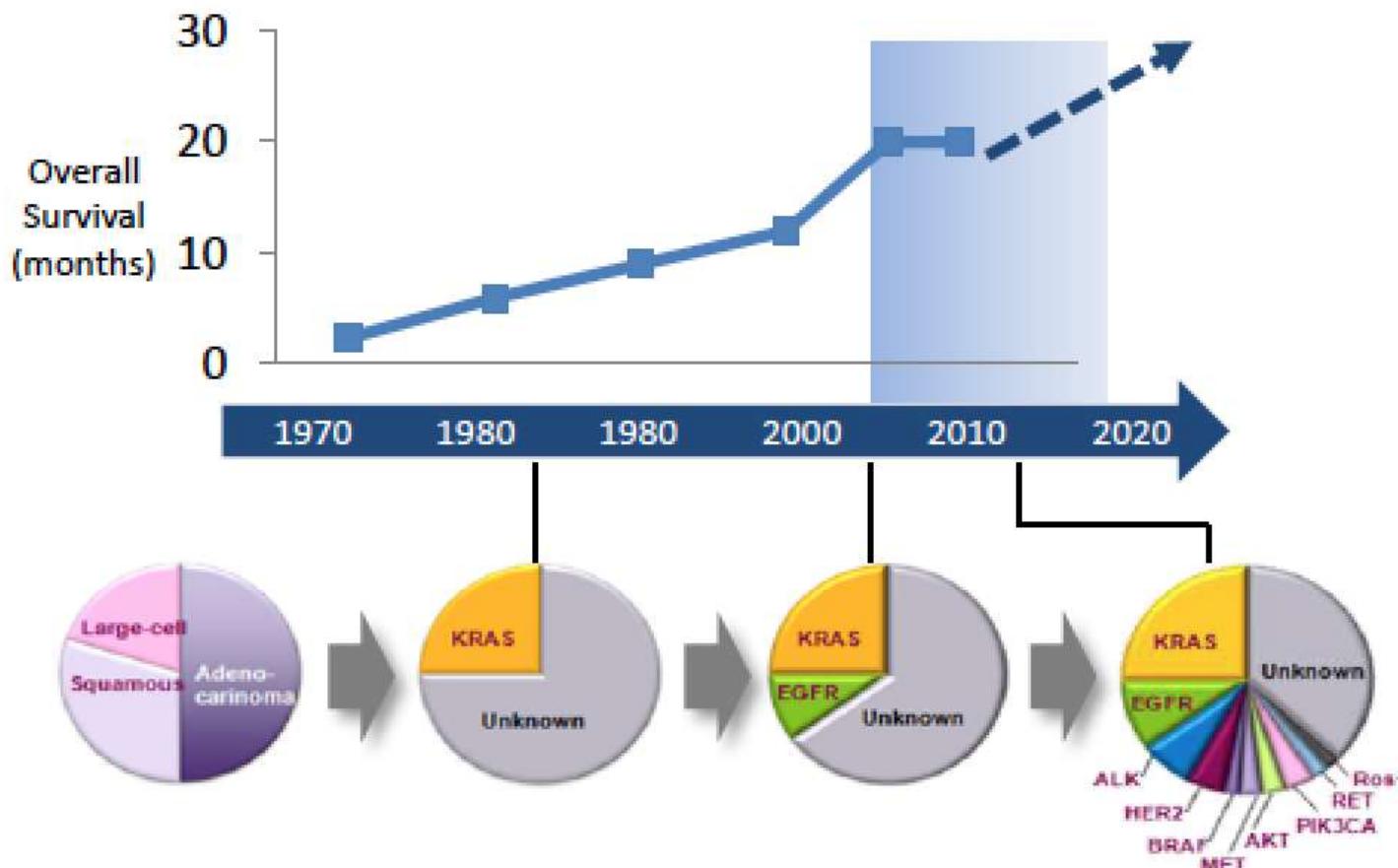
- Amgen
- Astra Zeneca
- Boehringer Ingelheim
- Bristol Meyers Squibb
- Celgene
- Eisai
- Incyte
- Ipsen
- Janssen
- Lilly
- Molteni
- MSD
- Novartis
- Pfizer
- Roche
- Foundation Medicine
- Nanostring

...

Targeted therapeutics are improving survival...

Example: NSCLC is an evolving landscape

3



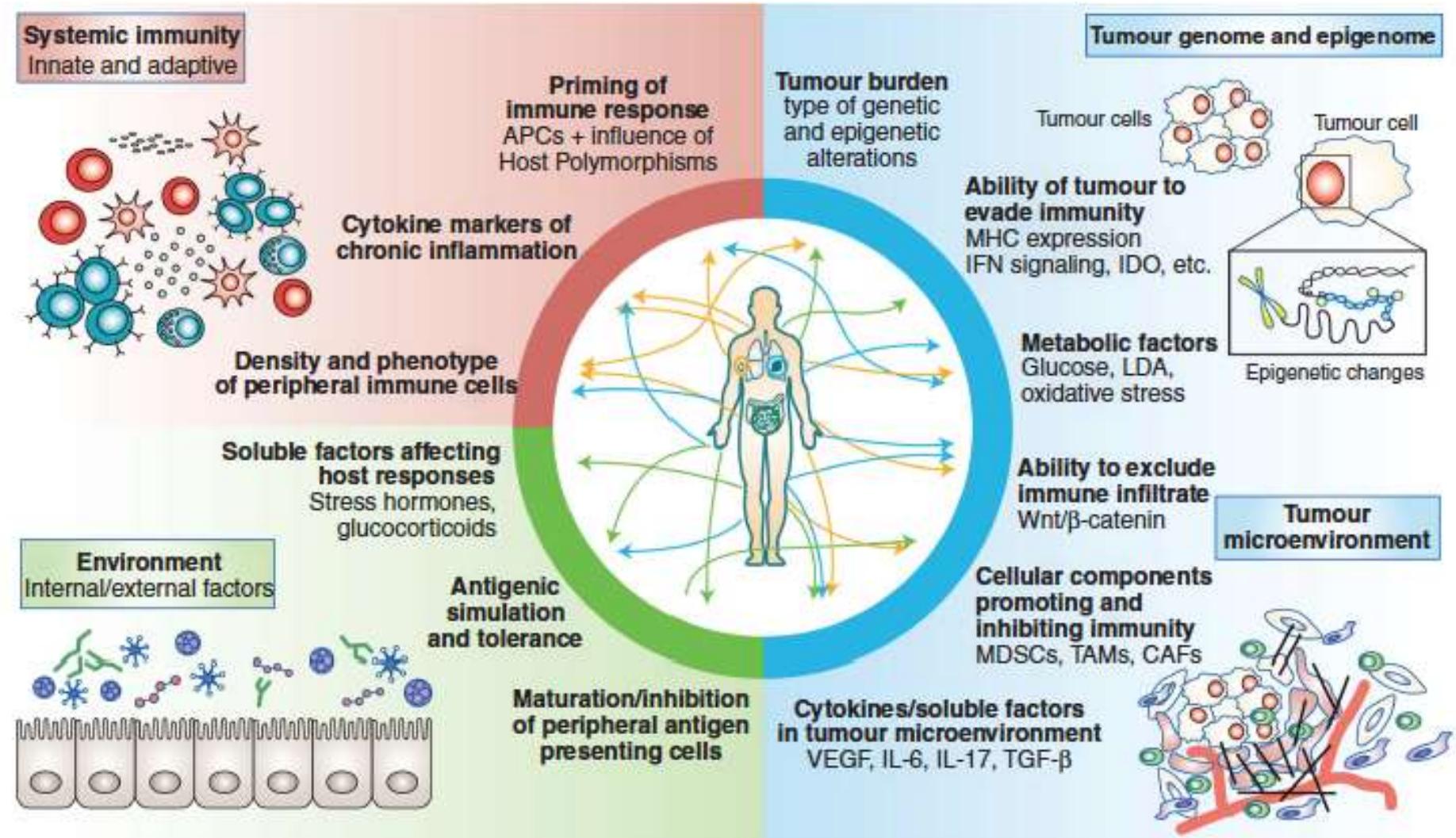
My Kingdom for a Biomarker!

According to a new market research¹, the cancer biomarkers market is projected to reach USD 20.48 Billion by 2022 from USD 11.53 Billion in 2017.

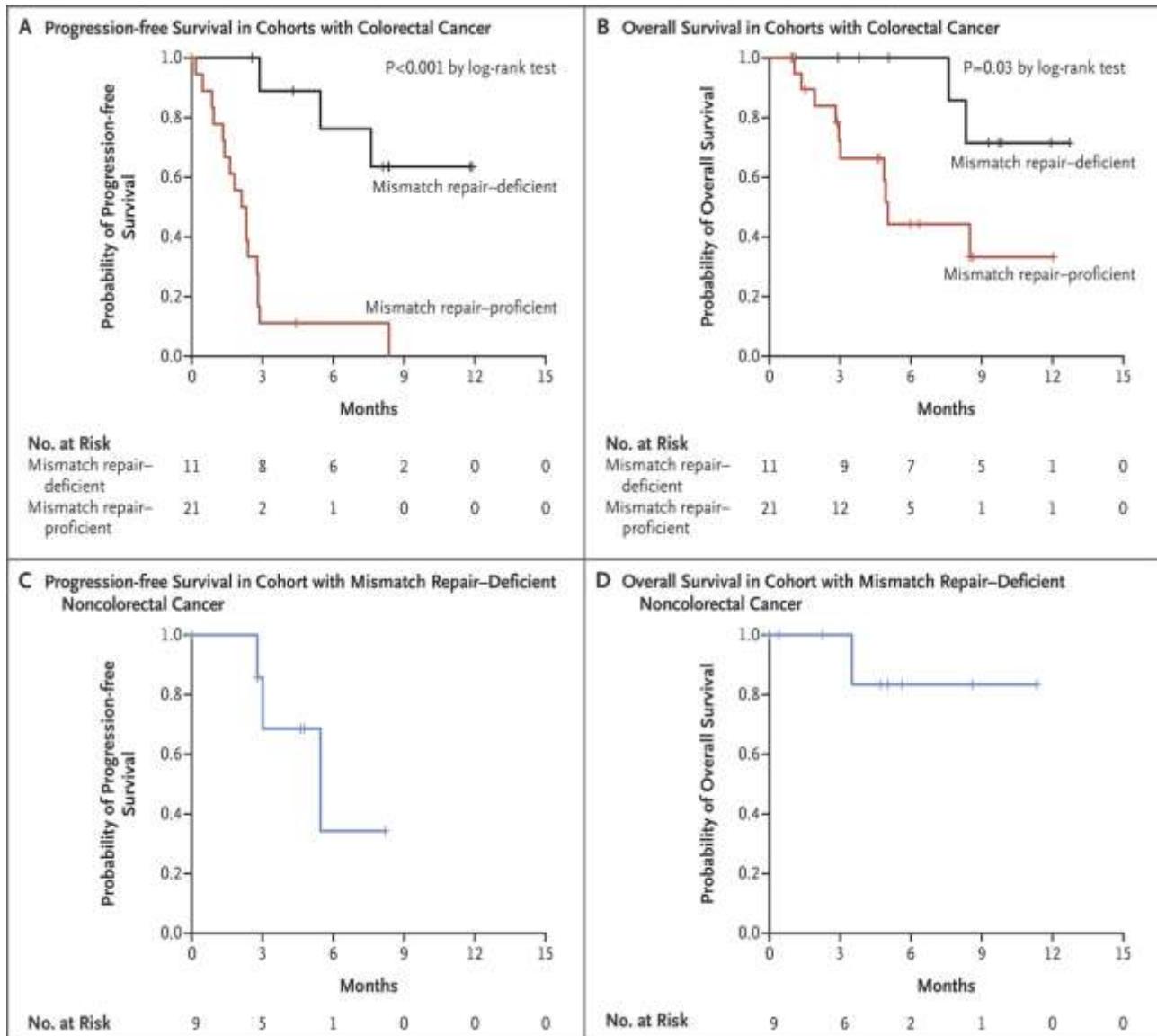
¹"Cancer Biomarkers Market by Type (Protein Biomarker, Genetic Biomarker), Cancer Type (Breast, Melanoma, Leukemia, Lung), Profiling Technology (Omics, Imaging, Immunoassay, Bioinformatics), Application (Diagnosis, Prognostics, R&D) - Global Forecast to 2022", Published by MarketsandMarkets™

The target is not (always) enough...

Immune parameters influencing response to immunotherapy



Clinical Benefit of Pembrolizumab Treatment According to Mismatch-Repair Status



TMB

The pros

- TMB is a biomarker of immunotherapy efficiency that is independent of PD-L1 IHC expression
- TMB can be efficiently assessed using targeted sequencing panels

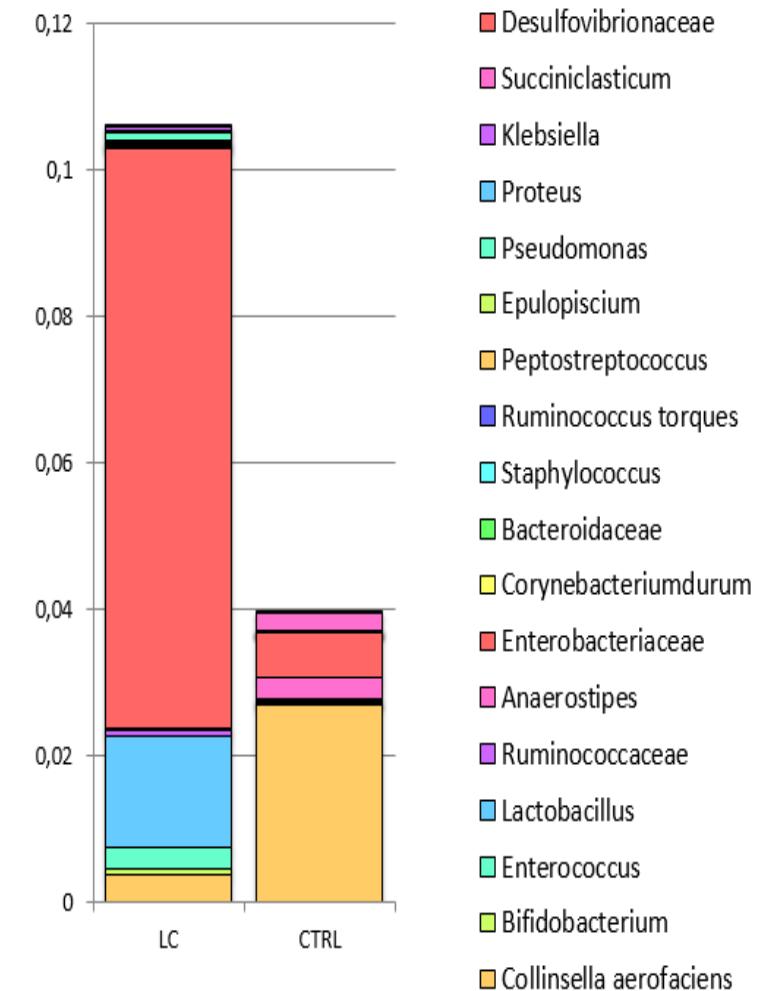
Sexual Dimorphism of Immune Responses: A New Perspective in Cancer Immunotherapy

 <i>Innate immunity</i>	 <i>Innate immunity</i>
↑ NK counts	↑ DC antigen presentation
↑ neutrophils mobility and inflammatory activity	↑ DC production of IFN γ
	↑ macrophages phagocytic activity
	↑ neutrophils phagocytic activity
	↑ MDSCs suppressive function
	↑ frequency of ILCs
 <i>Adaptive immunity</i>	 <i>Adaptive immunity</i>
↑ CD8+ T cell counts	↑ CD4+ T cell counts
↑ IL-17 production by CD4+ T cells	↑ activated and proliferating CD4+ T cells
↑ Treg cell counts	↑ IFN γ production by CD4+ T cells
↑ Th1 cell functions	↑ activated and proliferating CD8+ T cells
↓ B cell counts	↑ CD8+ T cell cytotoxic activity
↓ basal Ig	↑ CD4+/CD8+ T cell ratio
↓ antibody responses	↑ Th2 cell functions

CHANGES OF MICROBIOME PROFILE DURING NIVOLUMAB TREATMENT (very preliminary data)

Healthy controls/cancer patients

In NSCLC patients Rikenellaceae, Prevotella, Streptococcus, Lactobacillus ($p < 0.05$), Bacteroides plebeius, Oscillospira, Enterobacteriaceae ($p < 0.05$) appeared increased compared to CTRls.



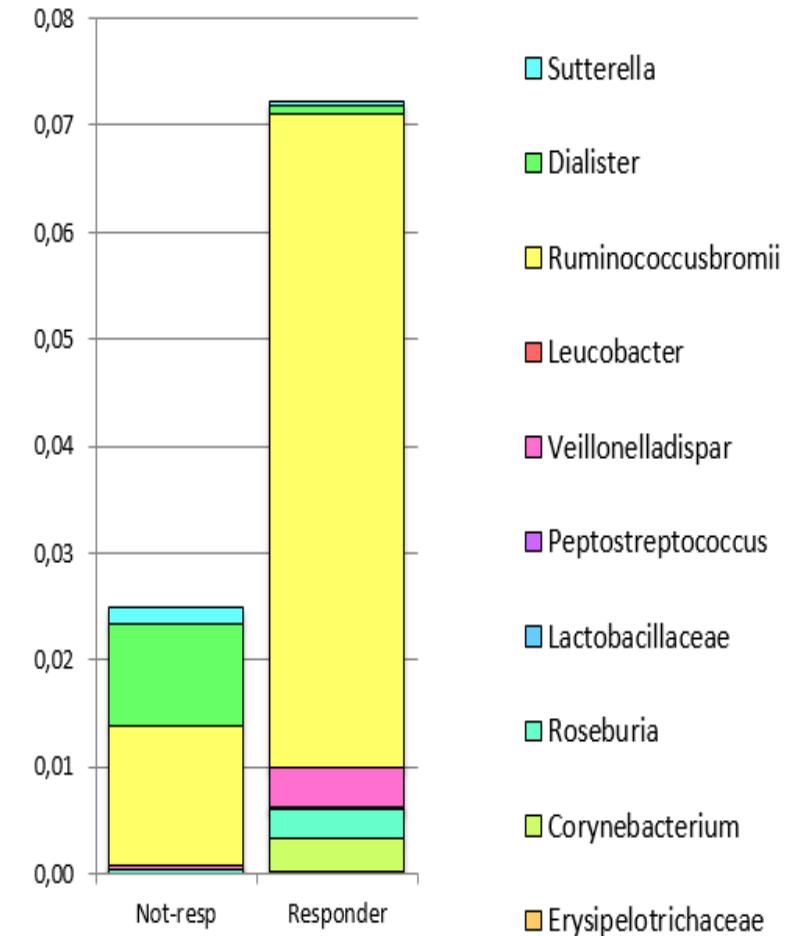
CHANGES OF MICROBIOME PROFILE DURING NIVOLUMAB TREATMENT (very preliminary data)

RESPONDERS VS NON RESPONDERS

Not responders had *Ruminococcus bromii*, *Dialister*, *Sutterella* more abundant than responder patients to therapy ($p < 0.05$).

Slightly increased in responders appeared *Akkermansia muciniphila*, *Bifidobacterium longum* and *Faecalibacterium prausnitzii* ($p < 0.05$). *Propionibacterium acnes*, *Veillonella*, *Staphylococcus aureus*, *Peptostreptococcus* appeared significantly over-expressed.

Kruskal-Wallis test at Genus/Species level (L6)



Dalla semplificazione osleriana alla complessità della malattia

La visione contemporanea della malattia risale al XIX secolo e si basa in gran parte sulla correlazione clinico-patologica osleriana, ossia sulla definizione della malattia in base al sistema d'organo in cui i sintomi sono manifesti e a cui la patologia è correlata, pur con il limite di generalizzare enormemente i *pato-fenotipi* di malattia.



Dalla semplificazione osleriana alla complessità della malattia

La malattia è raramente una semplice conseguenza dell'anomalia in un singolo prodotto genico, ma, piuttosto, è il riflesso di processi pato-biologici (genomici/deterministici e ambientali/stocastici), che interagiscono in una rete complessa per produrre un *pato-fenotipo* specifico per un determinato individuo in uno specifico momento.

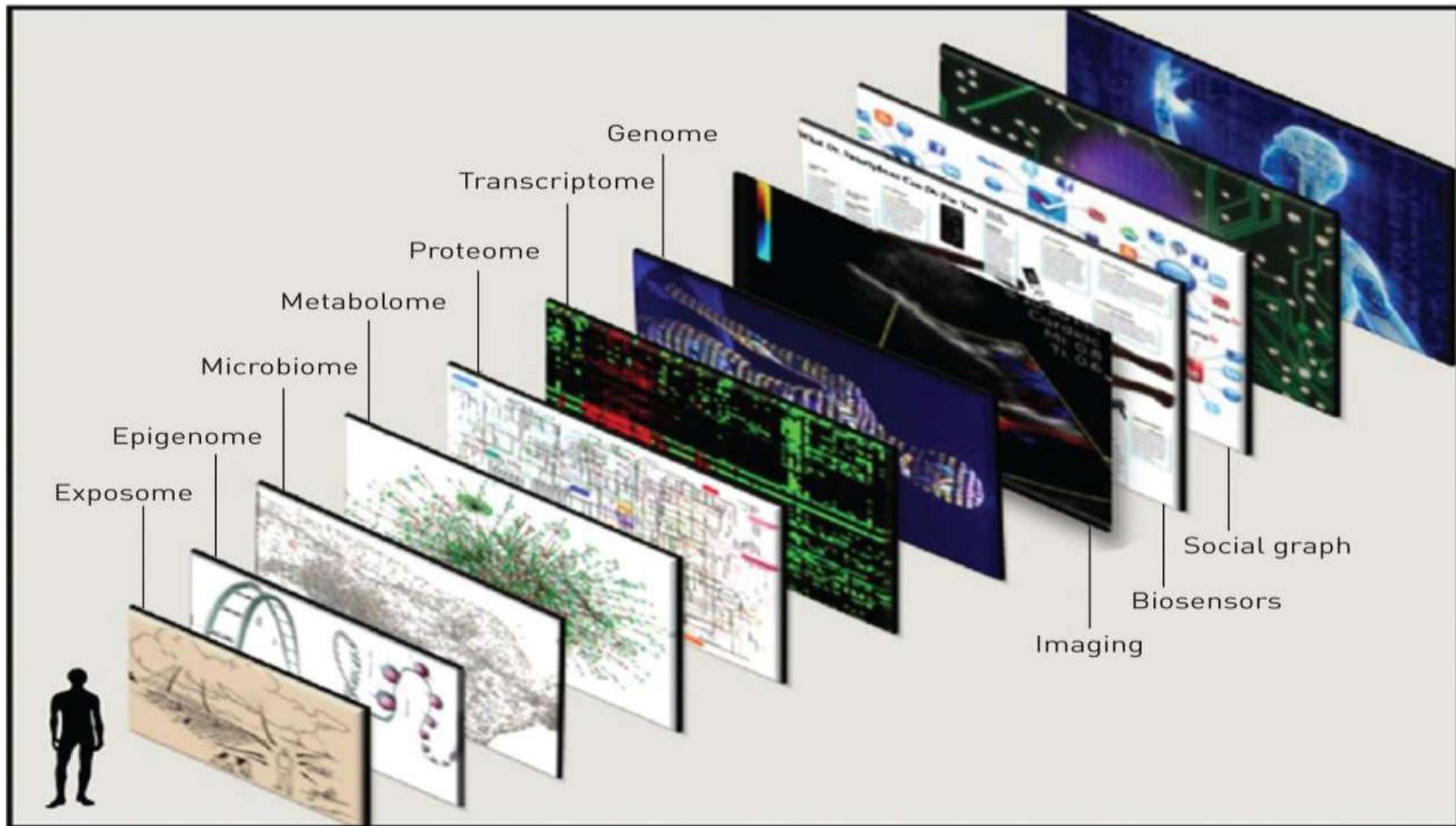


Biomarkers in the Age of Omics

Predicting response to checkpoint inhibitors beyond PD-L1 (or mutational burden and MSI)

- Limitations to biomarker discovery are not only technical or bioinformatic but conceptual as well:
 - First, the confusion stemming from the imposition of a ***pathology-type immunohistochemical marker*** (IHC) concept on omics data without fully understanding the characteristics and limitations of IHCs as applied in clinical pathology.
 - Second, the lack of serious consideration for the scope of ***disease heterogeneity***.
 - Third, the refusal of the biomedical community to borrow from ***other biological disciplines*** their well established methods for dealing with heterogeneity.

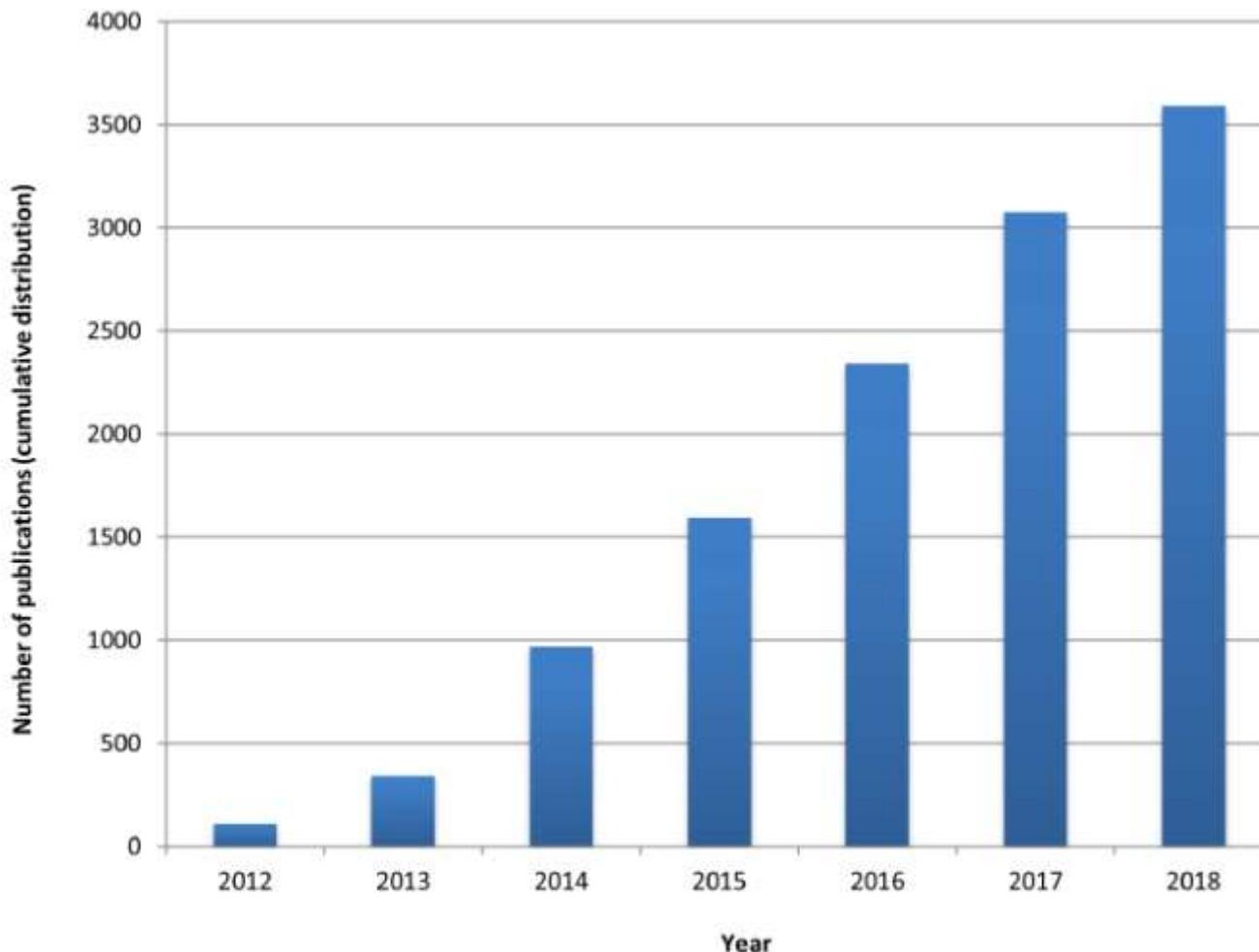
Multilevel layers of biological, environmental and social information ideally integrated in systems biomedicine approaches.



What is “Network Medicine”?

- The study of cellular, disease, and social networks which aim to quantify the complex interlinked factors contributing to individual diseases [...] by integrating genetic, genomic, biochemical, cellular, physiological, and clinical data to create a network that can be used to model predictively disease expression and response to therapy.
- ***It will, no doubt, revolutionize the science and practice of medicine.***

Number of 2012–2018 publications related to network-based approaches to medicine



What is “Network Medicine”?

- Medical researchers have long sought to identify single molecular defects that cause diseases, with the goal of developing ***silver-bullet therapies*** to treat them.
- But this paradigm overlooks the inherent complexity of human diseases and has often led to treatments that are inadequate or fraught with adverse side effects. Rather than trying to force disease pathogenesis into a reductionist model, network medicine embraces the complexity of multiple influences on disease and relies on many different types of networks: from the cellular-molecular level of protein-protein interactions to correlational studies of gene expression in biological samples.

Cosa è la malattia nella “*Network Medicine*”?

- Un modulo di malattia è definito come un gruppo di componenti di rete che contribuisce a determinare un fenotipo, la cui modificazione patologica porta a un particolare pato-fenotipo.
- Più precisamente, un modulo di malattia rappresenta una sottorete nella rete molecolare complessiva, in un insieme unico di interazioni sia prossimali che remote, capaci di condurre a un fenotipo anomalo, quando uno o più dei suoi componenti risulta essere disfunzionale.

Cosa è la malattia nella “*Network Medicine*”?

- Nonostante la gran mole di dati accumulati negli ultimi decenni, il numero delle interazioni funzionalmente rilevanti tra i componenti della rete resta in gran parte sconosciuto.
- Tale interconnessione a livello subcellulare implica che l'impatto di una alterazione genetica non si ripercuota solo sul prodotto di tale gene ma che l'effetto diffonda lungo i legami della rete, alterando l'attività dei prodotti genici che altrimenti non ne sarebbero interessati.
- ***Pertanto, l'impatto fenotipico di un difetto genico/proteico dipende dal contesto di rete.***

Cosa è la malattia nella “*Network Medicine*”?

- I network al momento più conosciuti e studiati sono quelli molecolari, ossia
 - network di interazione proteica (i cui nodi sono proteine legate tra loro da interazioni fisiche),
 - network metabolici (i cui nodi sono costituiti da metaboliti, legati tra loro se coinvolti nella stessa reazione biochimica),
 - network regolatori (i cui legami sono costituiti, a livello trascrizionale, dalla interazione regolatoria tra fattore trascrizionale e gene, mentre a livello post trascrizionale, i legami si stabiliscono tra chinasi e loro substrati),
 - network di RNA (i cui nodi sono costituiti da miRNAs e lncRNA).

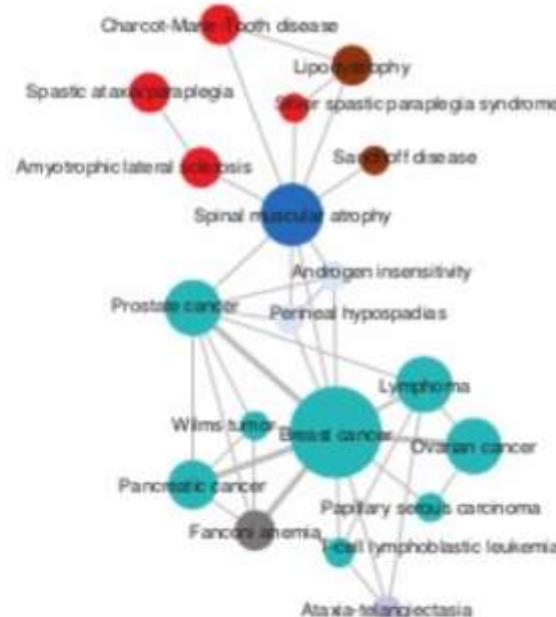
The human disease network

Kwang-Il Goh^{1,2,3}, Michael E. Cusick^{1,2}, David Valle¹, Barton Glick¹, Marc Vidal^{1,2,*}, and Albert-László Barabási^{1,2,3}
¹Center for Complex Networks and the Department of Physics, University of Notre Dame, Notre Dame, IN 46556; ²Center for Cancer Systems Biology (CCSB) and ³Department of Cancer Biology, St. Jude Children's Research Hospital, Memphis, TN 38103; ⁴Department of Genetics, Harvard Medical School, 325 Longwood Ave, Boston, MA 02115; ⁵Department of Physics, Korea University, Seoul 136-701; ⁶Institute of Genetics and Department of Radiation and the Institute of Molecular Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21201

Edited by H. Eugene Nazyro, Boston University, Boston, MA, and approved April 3, 2007 (version received February 14, 2007)

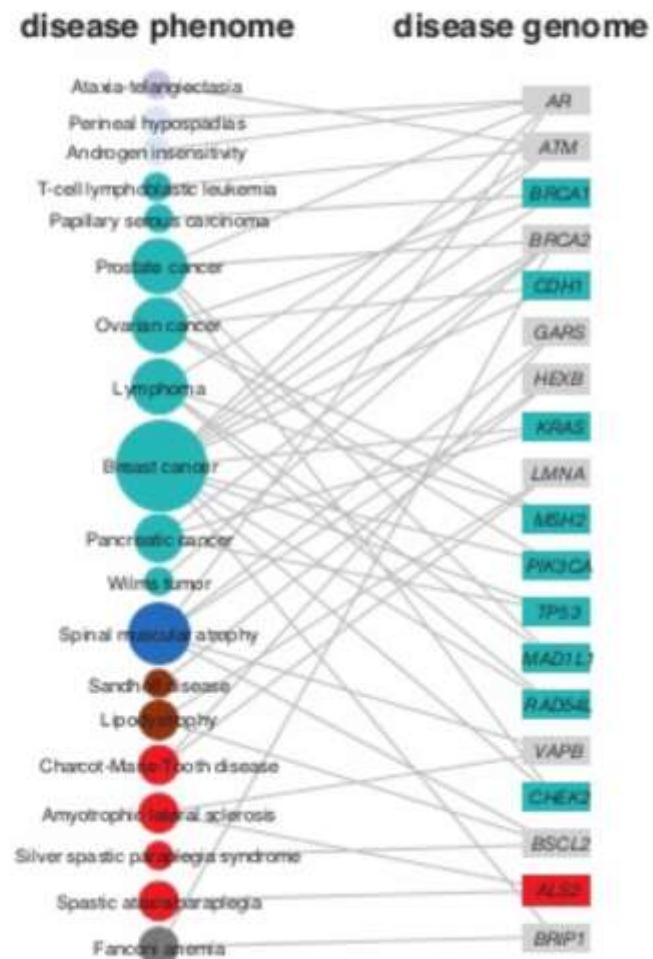
Goh et al., PNAS 2007

Human Disease Network (HDN)

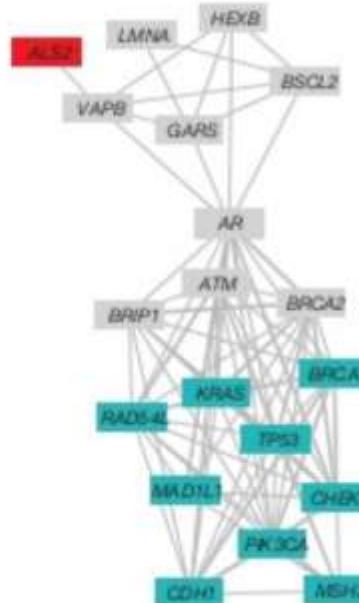


Diseases as network perturbations

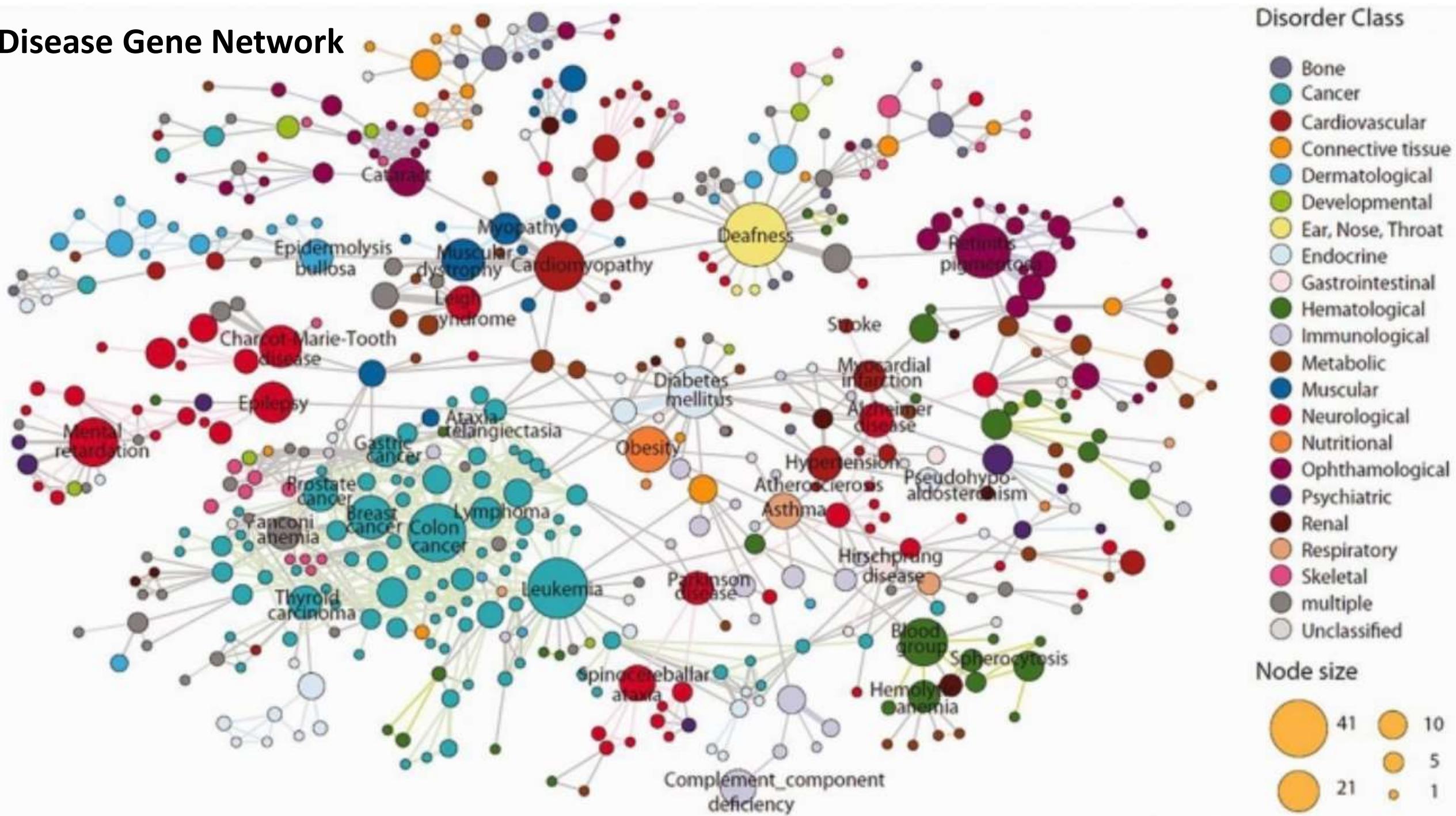
DISEASOME



Disease Gene Network (DGN)

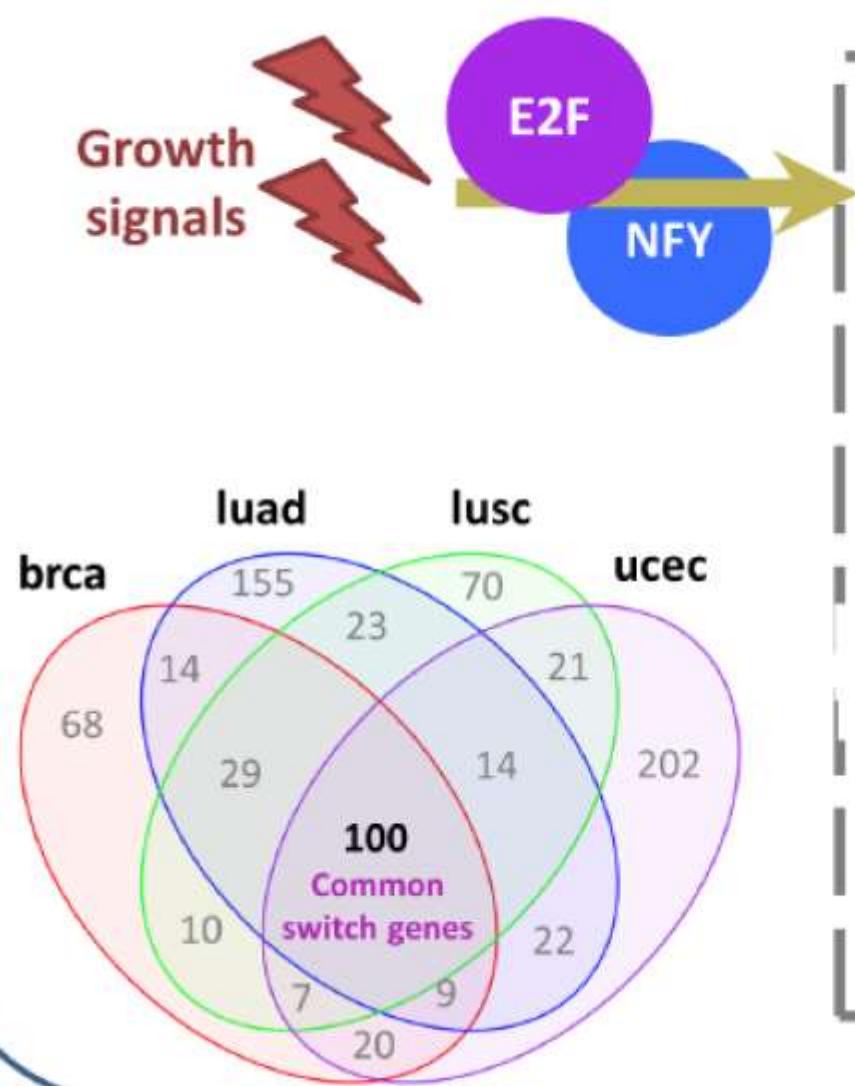


Disease Gene Network



The switch gene regulation mechanism in human cancers

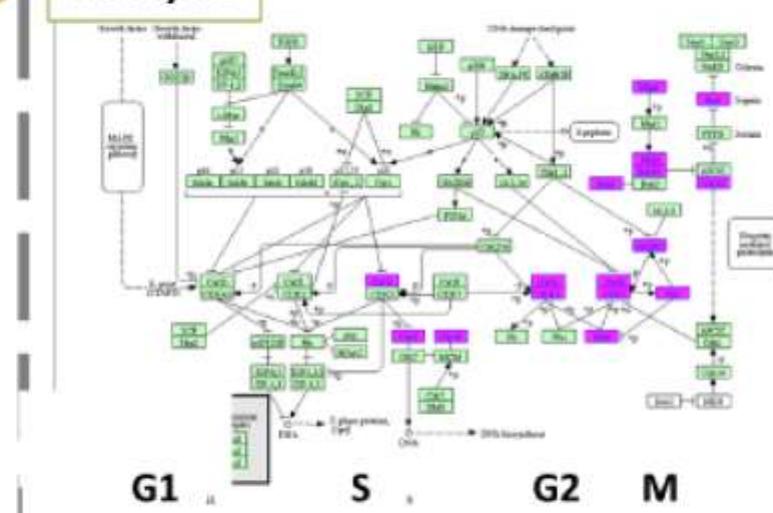
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Multi-cancer analysis

Cancer switches

cell cycle

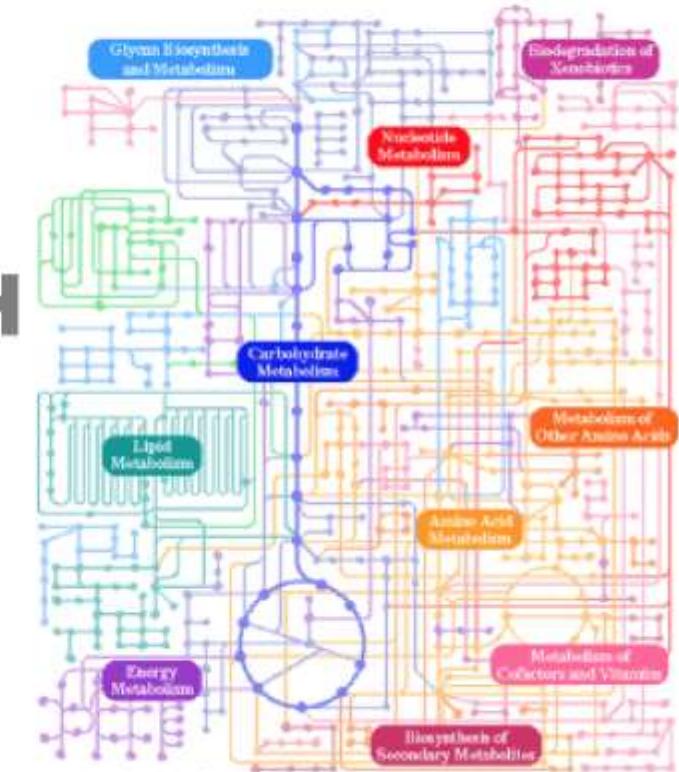


E2F

NFY

G2/M transition

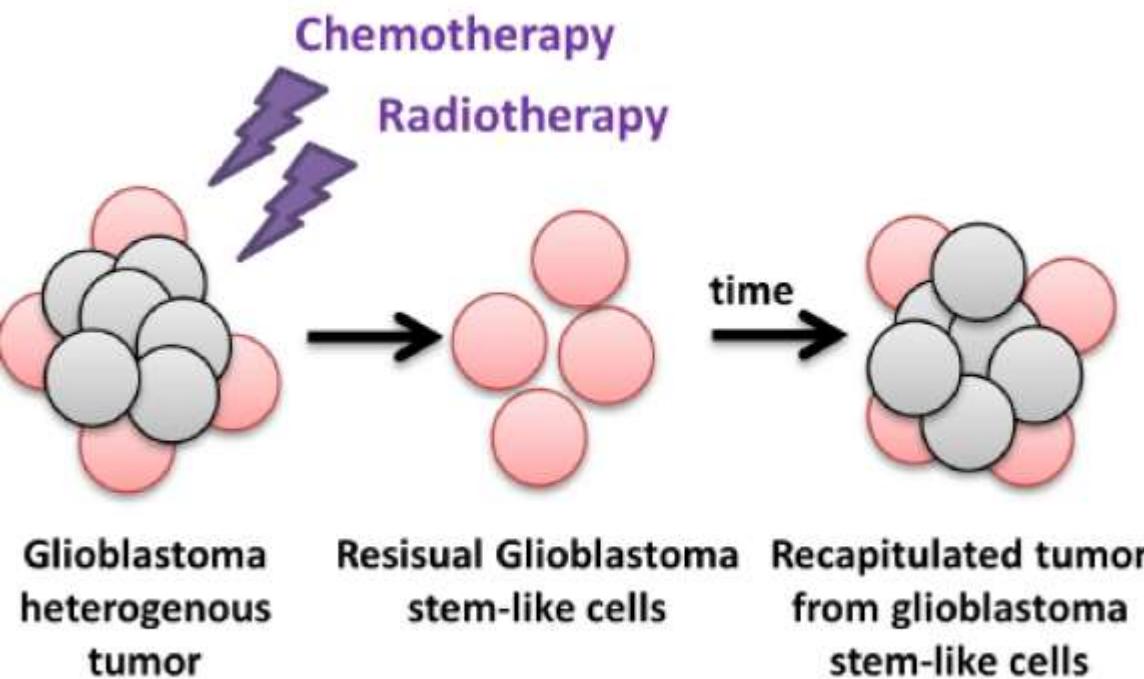
Nearest neighbors of cancer switches



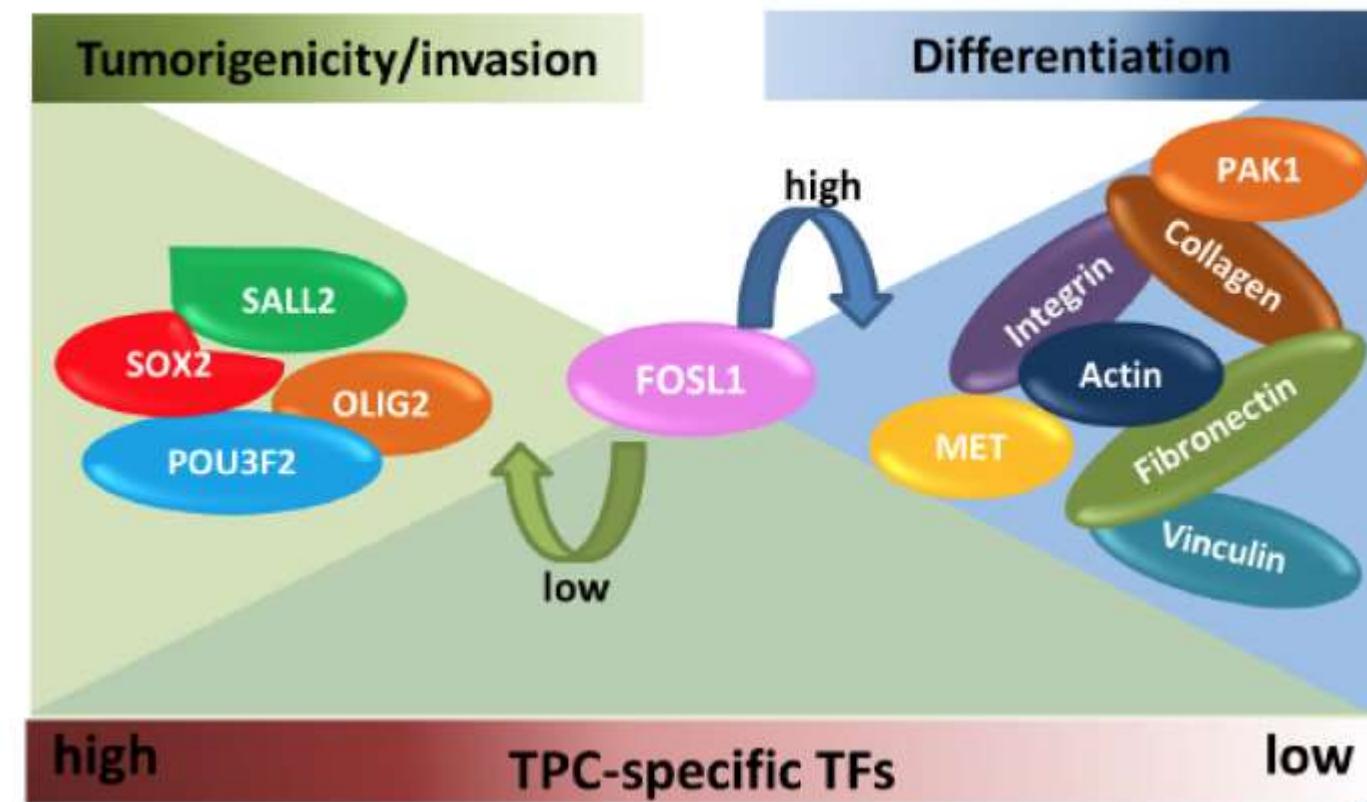
Metabolic pathways

The switch gene regulation mechanism in human glioblastoma

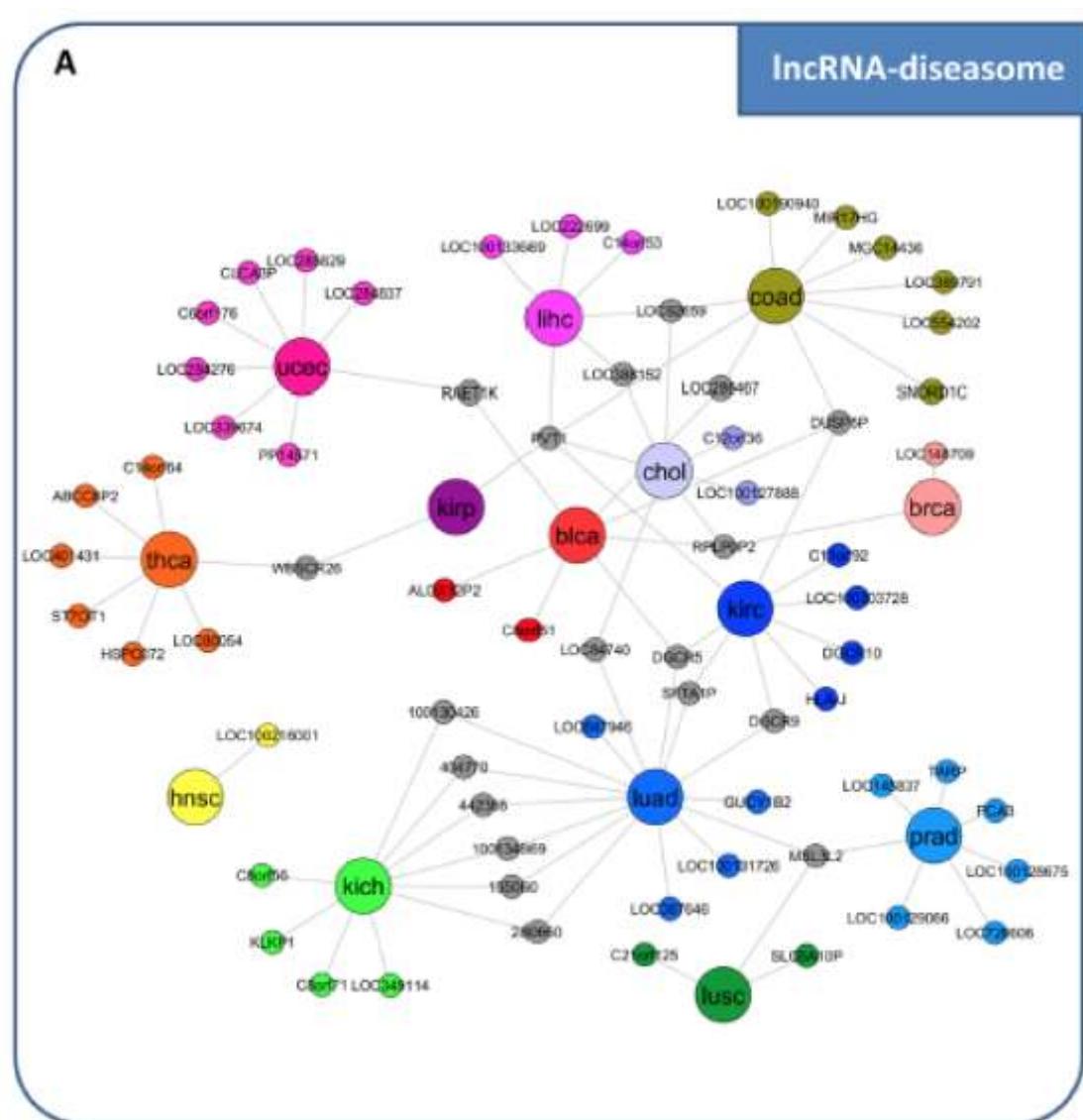
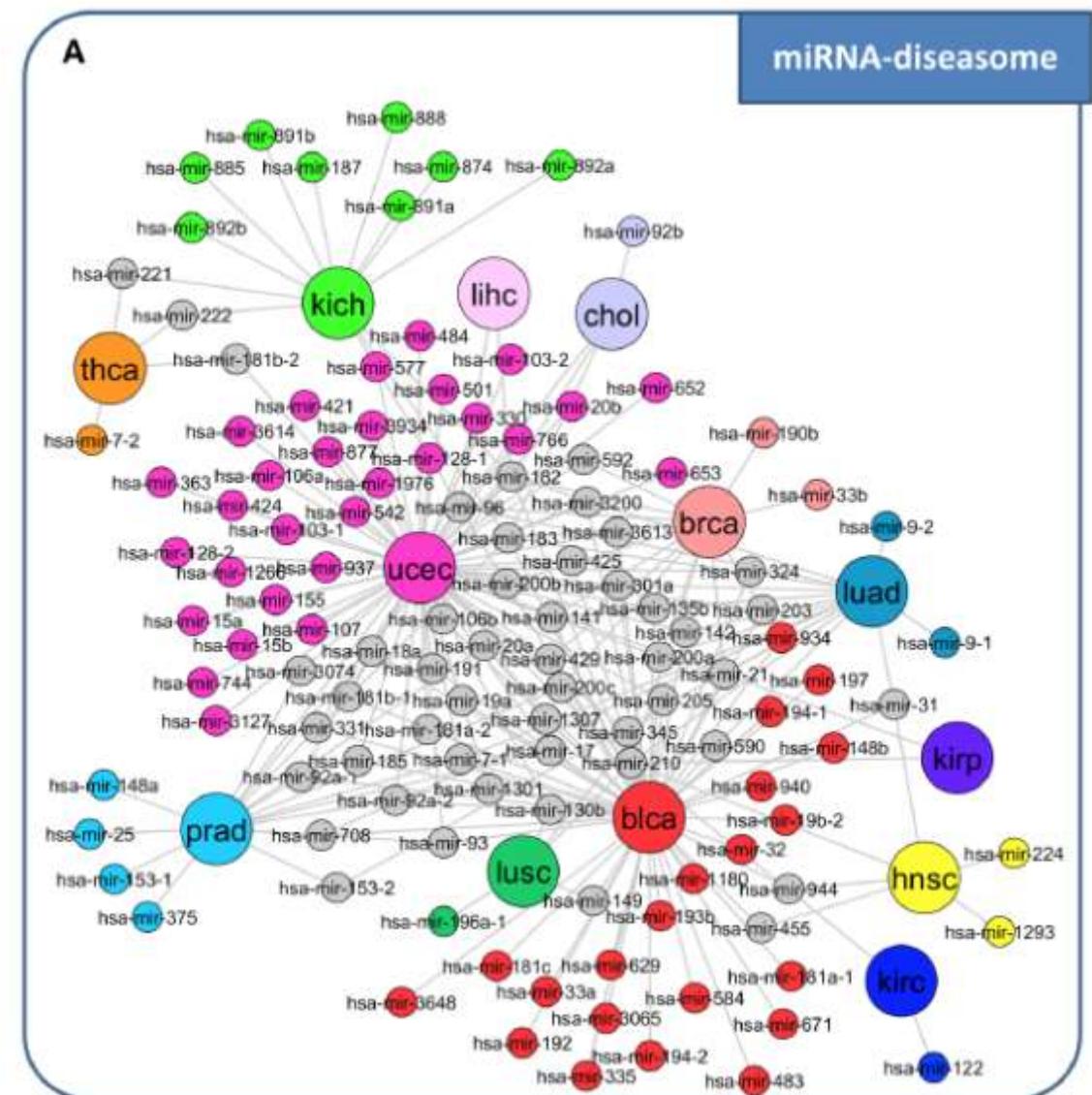
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Glioblastoma analysis



Analysis of miRNAs and lncRNAs acting as switch genes

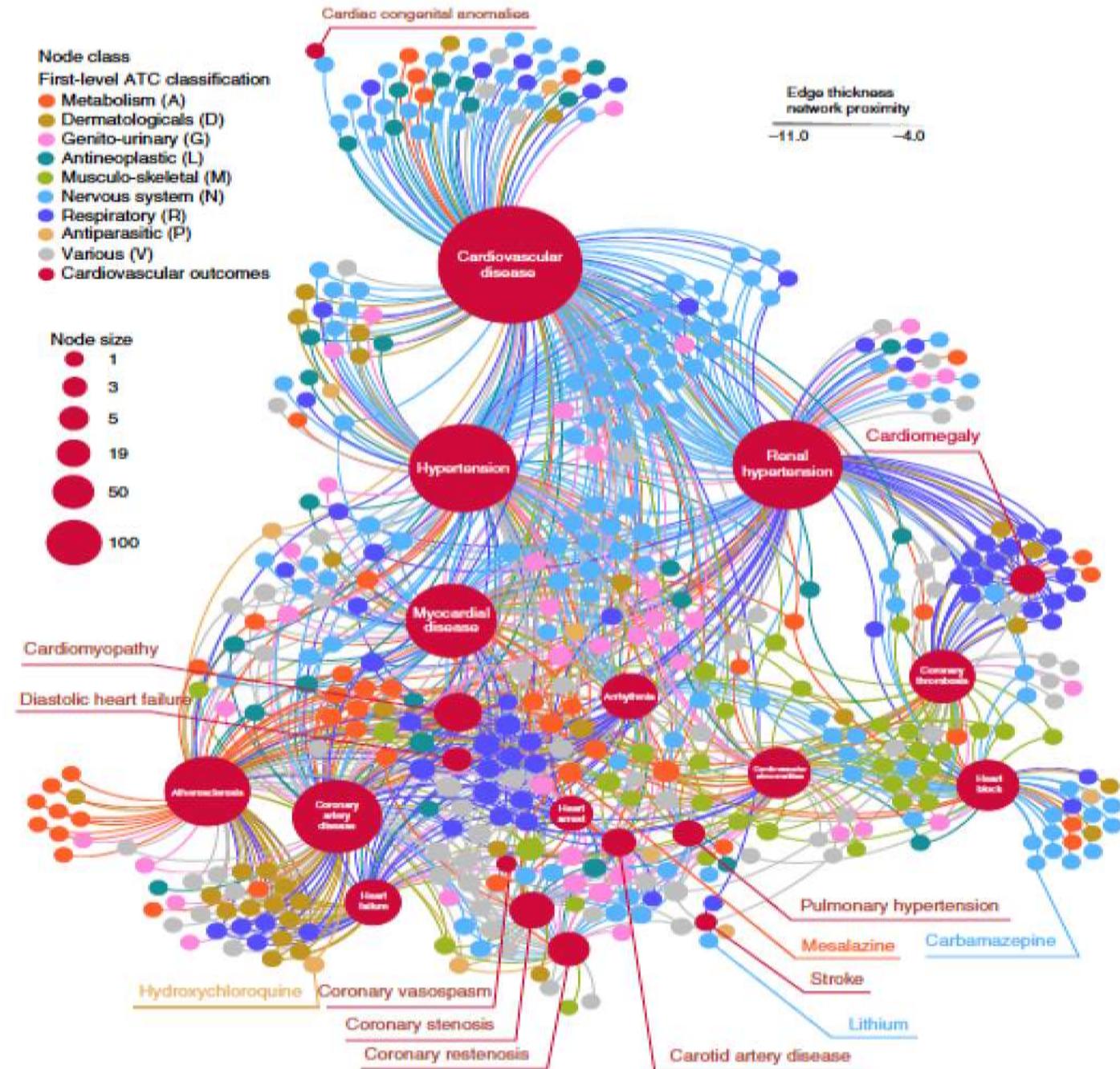


The predicted drug-disease network.

The predicted drug-disease association network connects 22 types of cardiovascular disease and 431 FDA-approved non-cardiac drugs.

An integrated, mechanism-based human protein–protein interactome strategy can successfully uncover novel drug-disease indications, undesirable side effects, and potential mechanisms for these actions of approved drugs, addressing a crucial issue in drug development and patient care.

F Cheng, R J. Desai, D E. Handy, R Wang, S Schneeweiss, A-L Barabási & J Loscalzo NATURE COMMUNICATIONS (2018) 9:2691



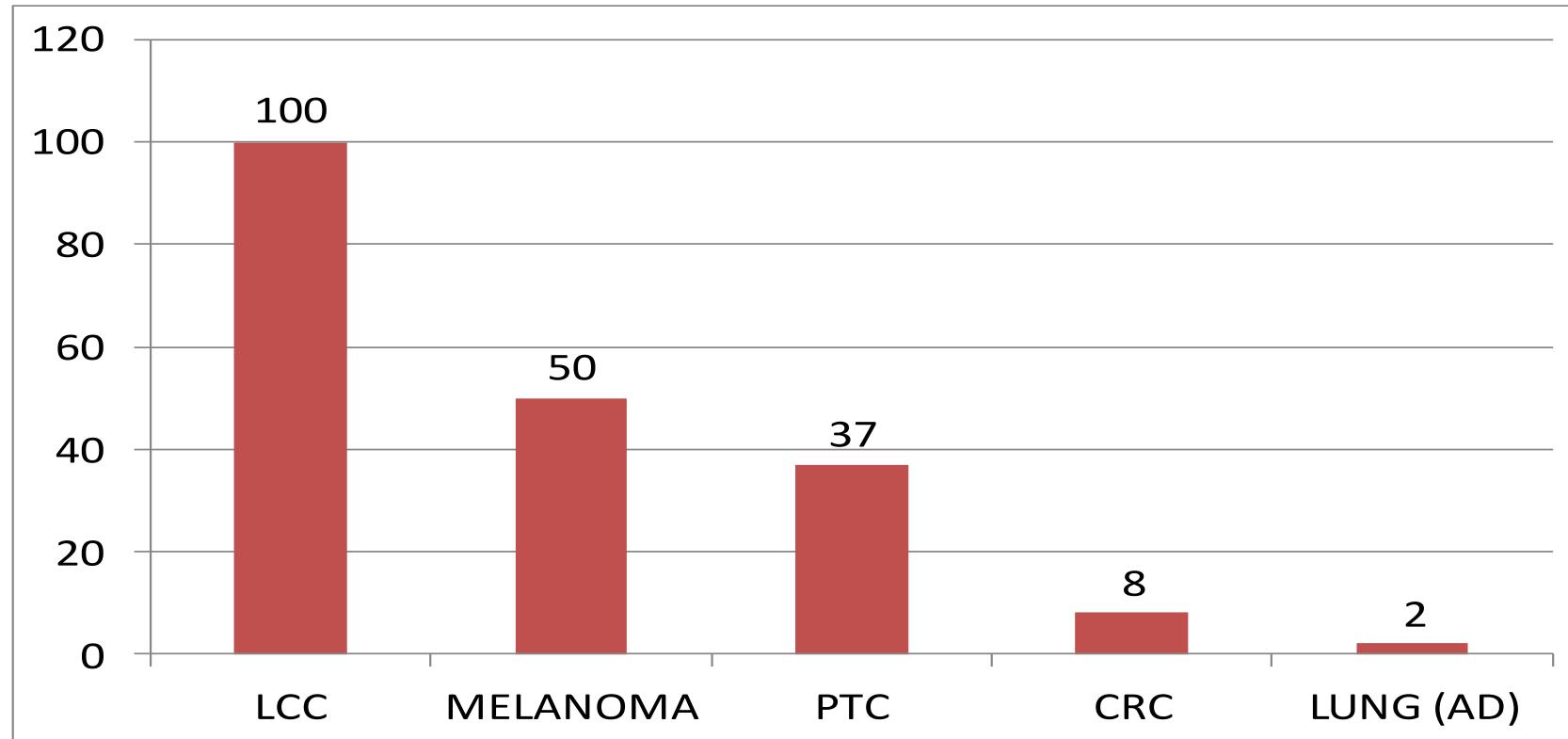
La mutazione di B-RAF

- Gli eventi mutazionali non sono tutti ugualmente rilevanti ed il loro impatto clinico è funzione anche del contesto che li ospita.

Frequenza mutazione BRAF V600E in vari tumori

Tumori con mutazione BRAF V600E:

- Melanoma
- Leucemia cellule capellute (LCC)
- PTC (tiroide)
- Adenoca polmonare
- Adenoca colon-retto (CRC)
- Ca sieroso ovaio
- Mieloma multiplo
- Glioblastoma
- Ca endometrio
- Ca mammella



Variabilità della risposta al vemurafenib nei tumori con mutazione BRAF V600E

CANCRO	ORR (%)
LCC	96-100
Melanoma	51
Tiroide	38.5
NSCLC	33
Colon	4.8

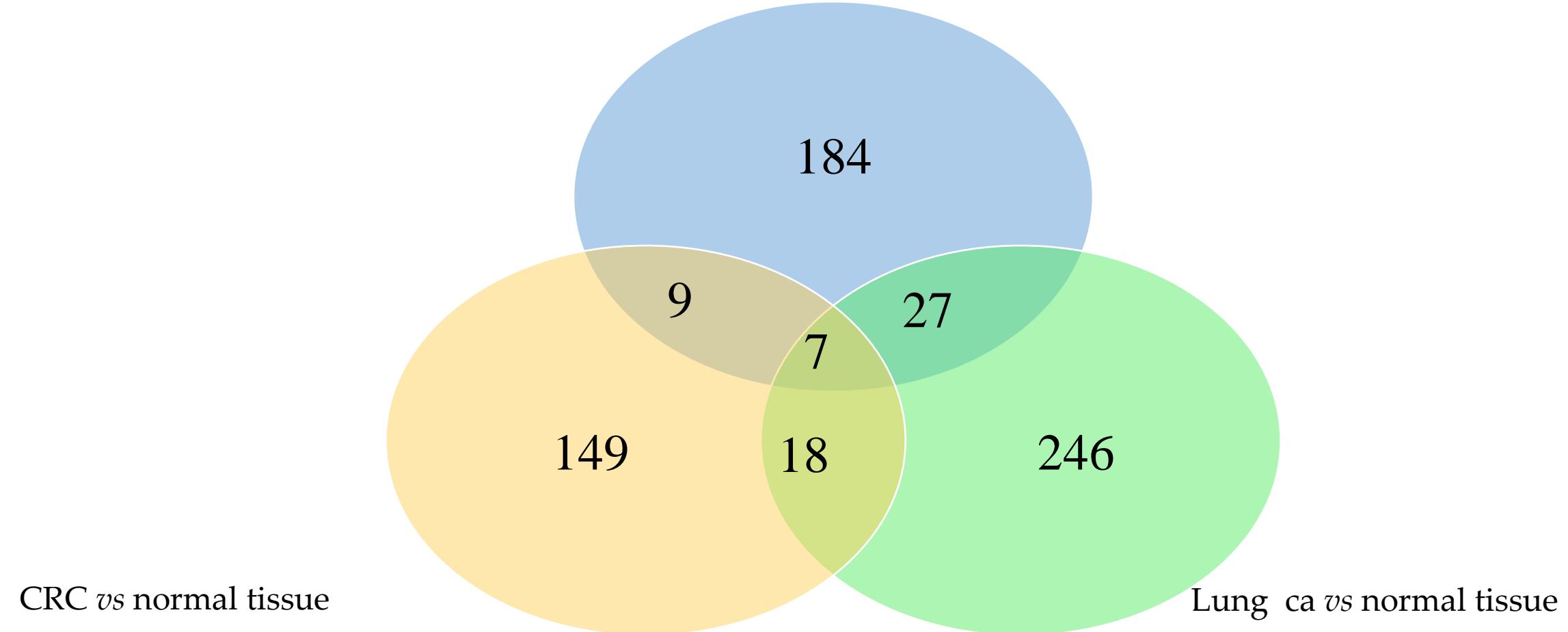
Chapman PB et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. BRIM-3 Study Group. N Engl J Med. 2011

Tiacci E et al. Targeting Mutant BRAF in Relapsed or Refractory Hairy-Cell Leukemia. N Engl J Med. 2015

Kopetz S et al. Phase II Pilot Study of Vemurafenib in Patients With Metastatic BRAF-Mutated Colorectal Cancer. J Clin Oncol. 2015

Venn diagram showing shared and non-shared switch genes for each BRAF V600E cancer compared to its normal tissue.

Thyroid ca *vs* normal tissue

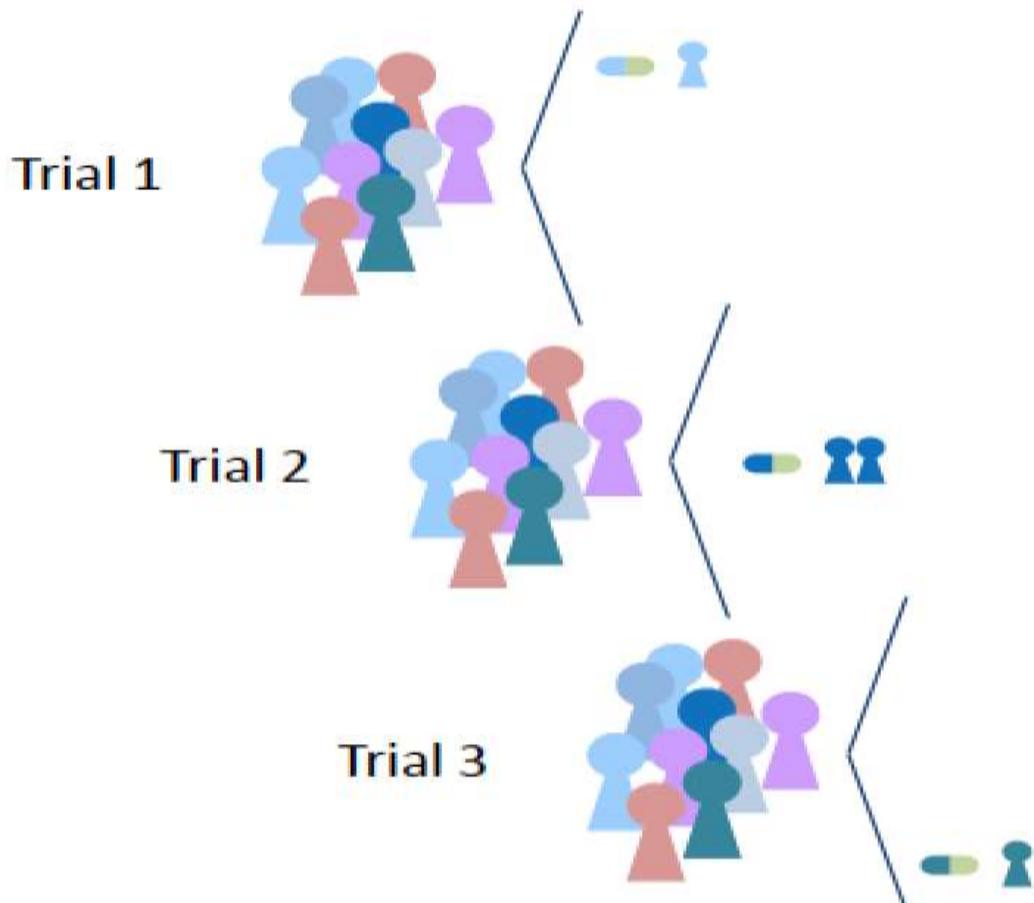


CRC *vs* normal tissue

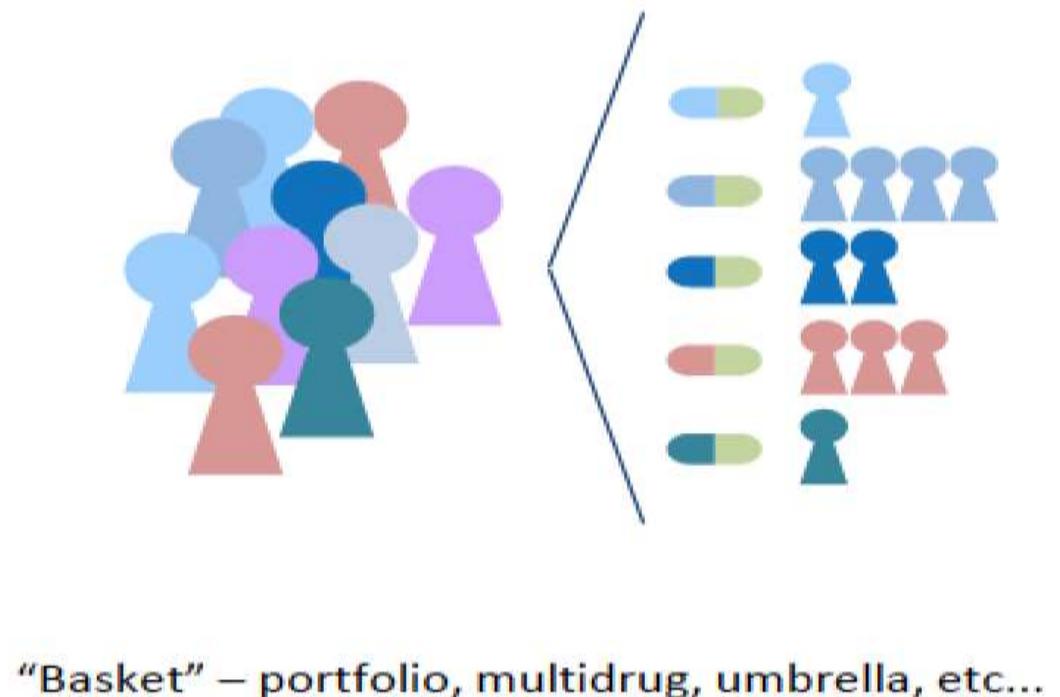
Lung ca *vs* normal tissue

The ROME trial: *from histology to target* A multi-basket trial

Choosing the patient for the trial



“Baskets” – choose the trial for the patient





The ROME trial: *from histology to target*

Prospective Randomized 2 arms Phase II trial:

Therapy at choice of physician (TCP) vs Tailored treatment (TT)

Pts affected by progressive disease

Patient with recurrent/metastatic breast, gastrointestinal cancer (excluding colon-rectal cancer), lung cancer or other neoplasia, excluding *in first line* patients with well-established actionable targets for which approved and marketed targeted drugs are available (i.e. lung cancer with EGFR mutation, or ALK translocation, B-RAF mutant melanoma, GIST with KIT mutations or breast cancer with HER2 amplification).

Patients must have biopsable lesion to perform Foundation One evaluation and will be randomized to targeted therapy vs SOC

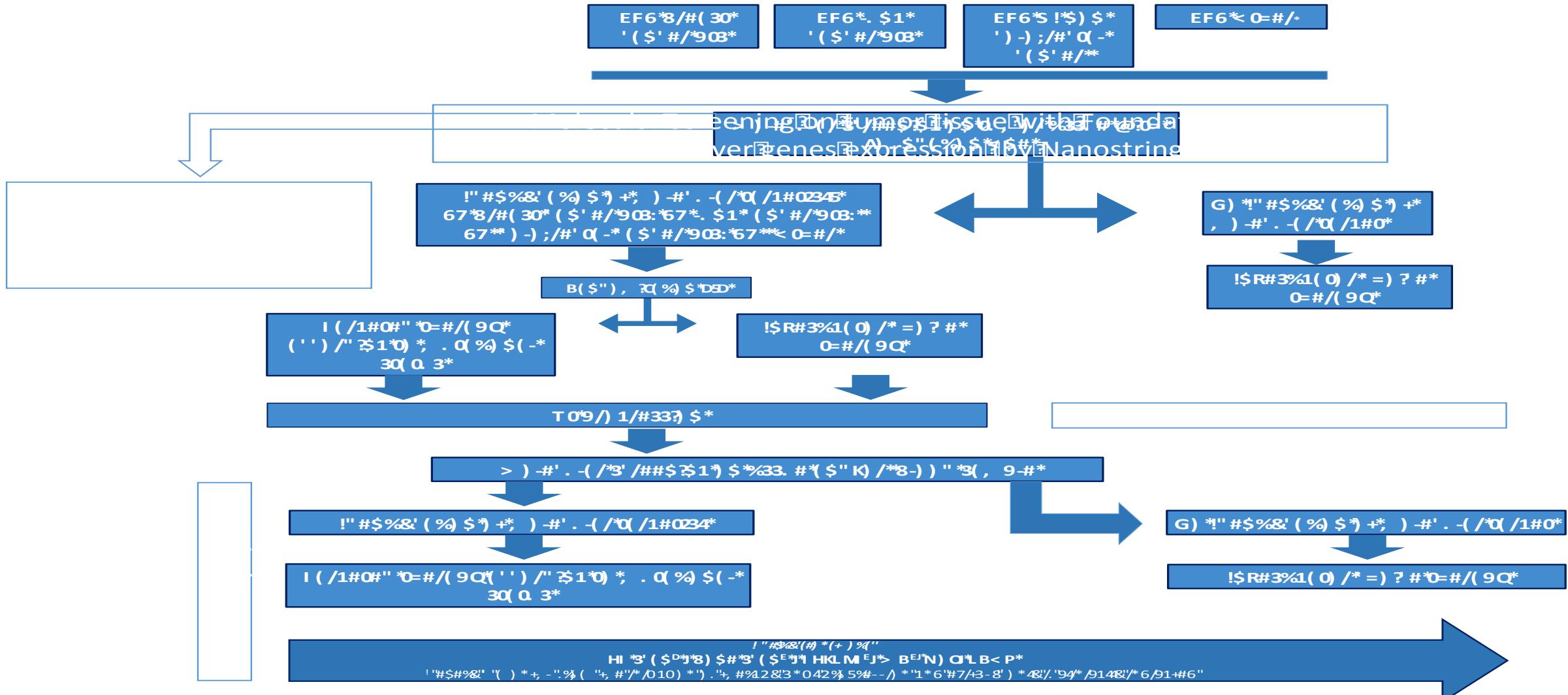
Primary endpoint: ORR of TCP vs TT (RECIST v1.1 criteria)

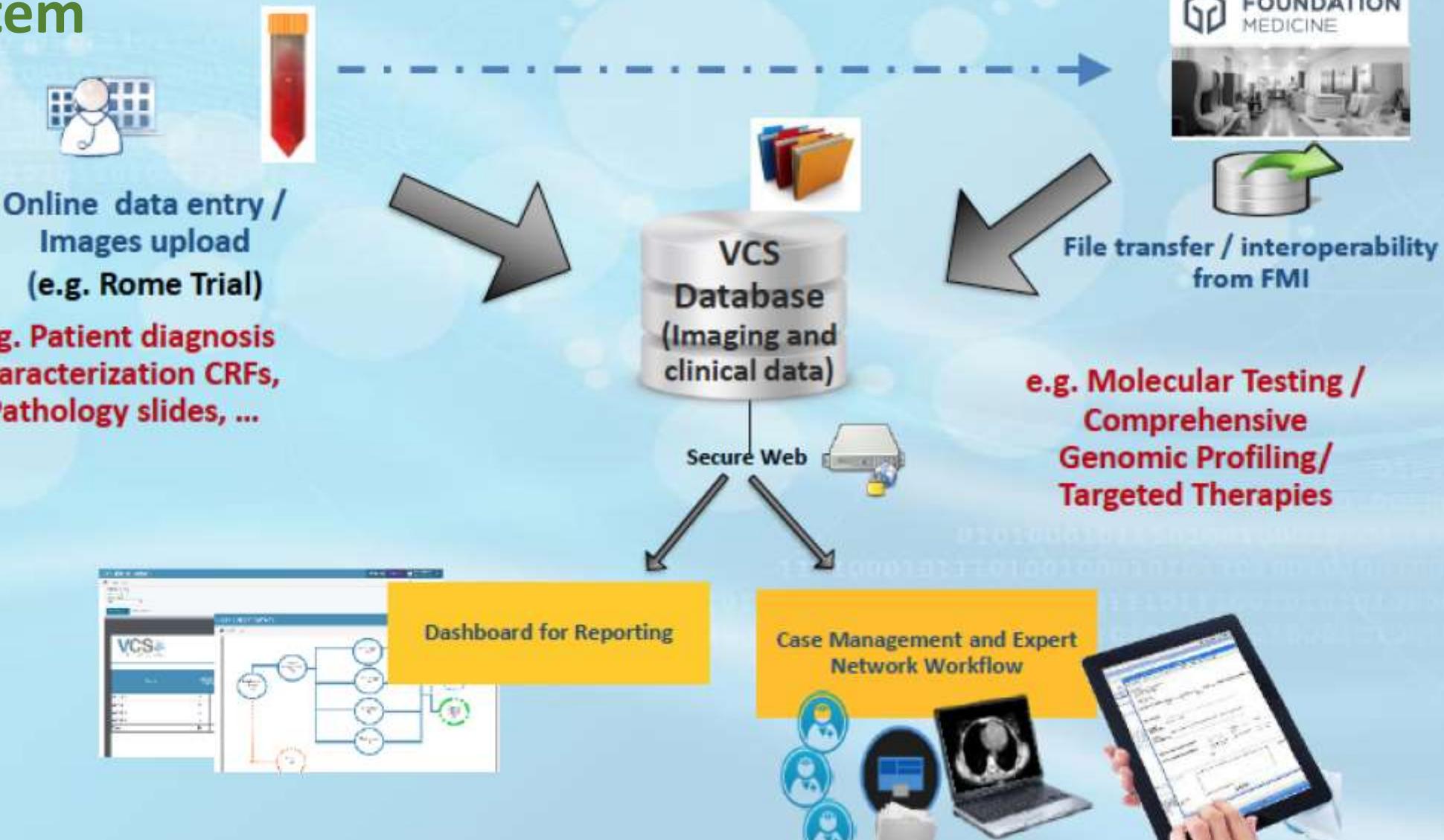
Secondary Endpoint:

OS of TCP vs TT , TTF, TTNT

The ROME trial: *from histology to target* A multi-basket trial in 39 Centers in Italy

The ROME trial: *from histology to target*



Proposal: VCS Structure for
Molecular Tumor Board

Conclusions

- In the last decade, the great advances in high-throughput technologies have led to massive amounts of genomic, transcriptomic, proteomic and metabolomic data capable to provide new opportunities for identifying potential biomarkers and developing effective treatments for human diseases.
- The availability of this huge amount of data has revolutionized biomedical science and, in particular, cancer genomics, but only the amount is not enough.
- The network medicine could become the solution.