ASU Complex Adaptive Systems Initiative
Arizona State University

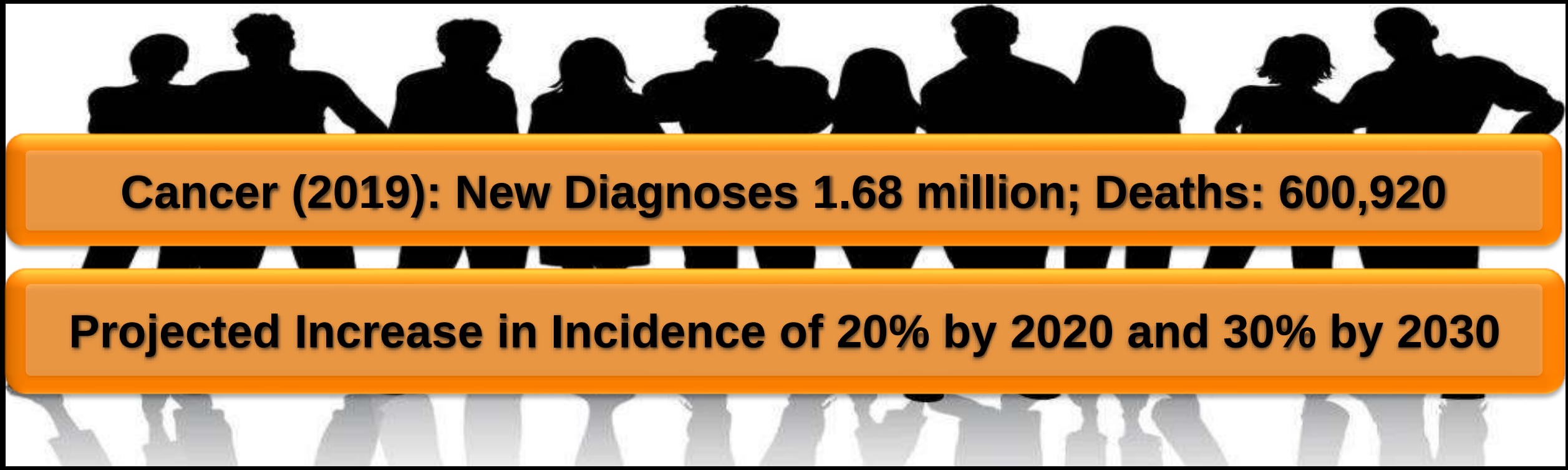
Molecular Med TRI-CON
March 10-15, 2019 ▼ San Francisco, CA
MOSCONE SOUTH CONVENTION CENTER

Development of Multi-Parameter Assays to Predict Therapeutic Response in Cancer Immunotherapy

Dr. George Poste
Chief Scientist, Complex Adaptive Systems Initiative
and Regents Professor of Health Innovation
Arizona State University
george.poste@asu.edu
www.casi.asu.edu

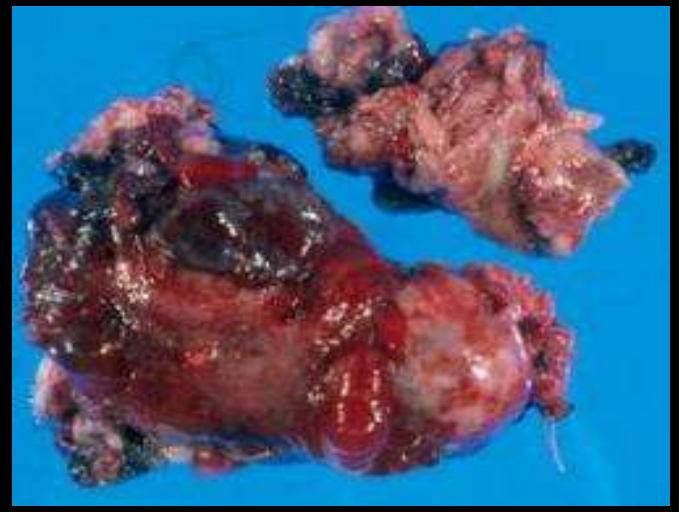
26th International Molecular Med TRI-CON
March 12, 2019 San Francisco, CA
Moscone South Convention Center

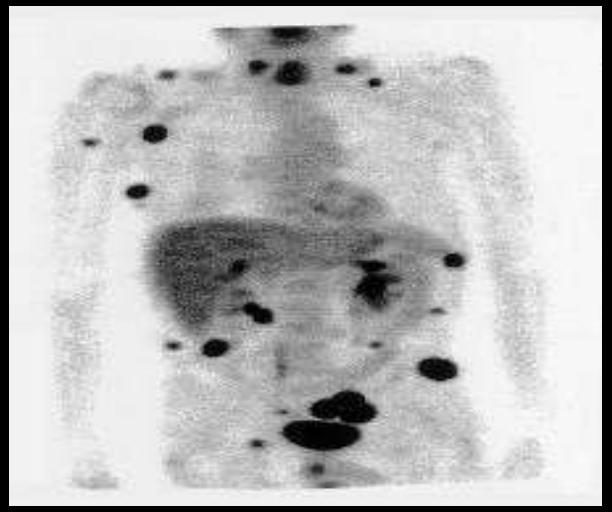
Confronting the Clinical, Economic and Human Toll of Cancer

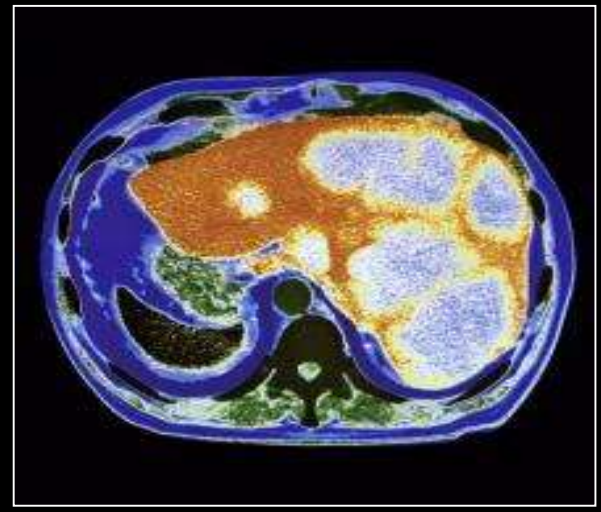


Cancer (2019): New Diagnoses 1.68 million; Deaths: 600,920

Projected Increase in Incidence of 20% by 2020 and 30% by 2030







Realizing the Promise of Cancer Immunotherapy

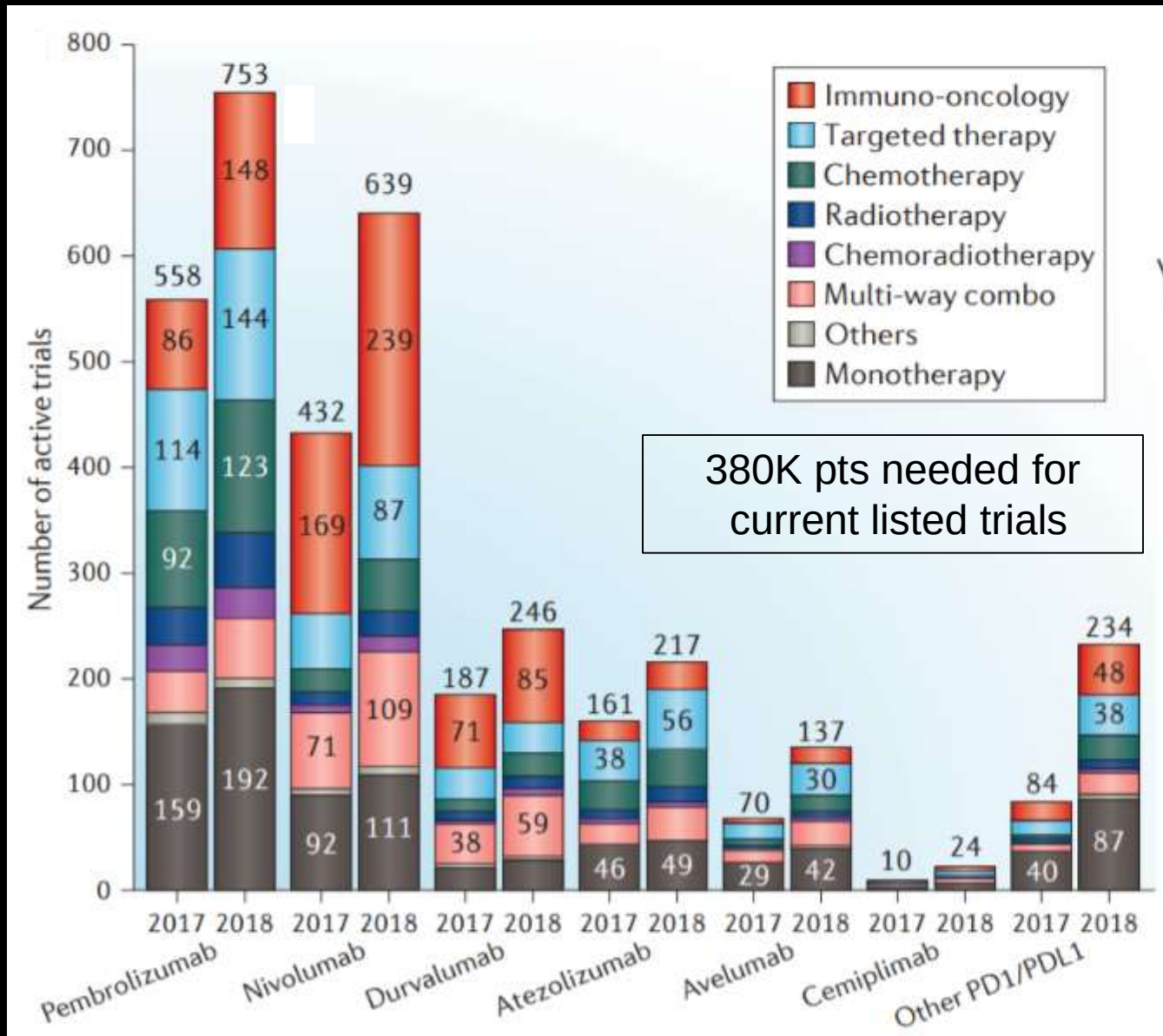
- wide variation in Rx response rates
  - only 20 - 40% positive responses even in most responsive malignancies
  - even lower percentage of clinically durable responses (KM long tail)
- improve response rates across all malignancies
- management of serious AEs (CRS, autoimmune)
- will I/O combination regimens increase response rates?
- rationale for selection of combination regimens
- unsustainable long term cost of treating non-responder patients

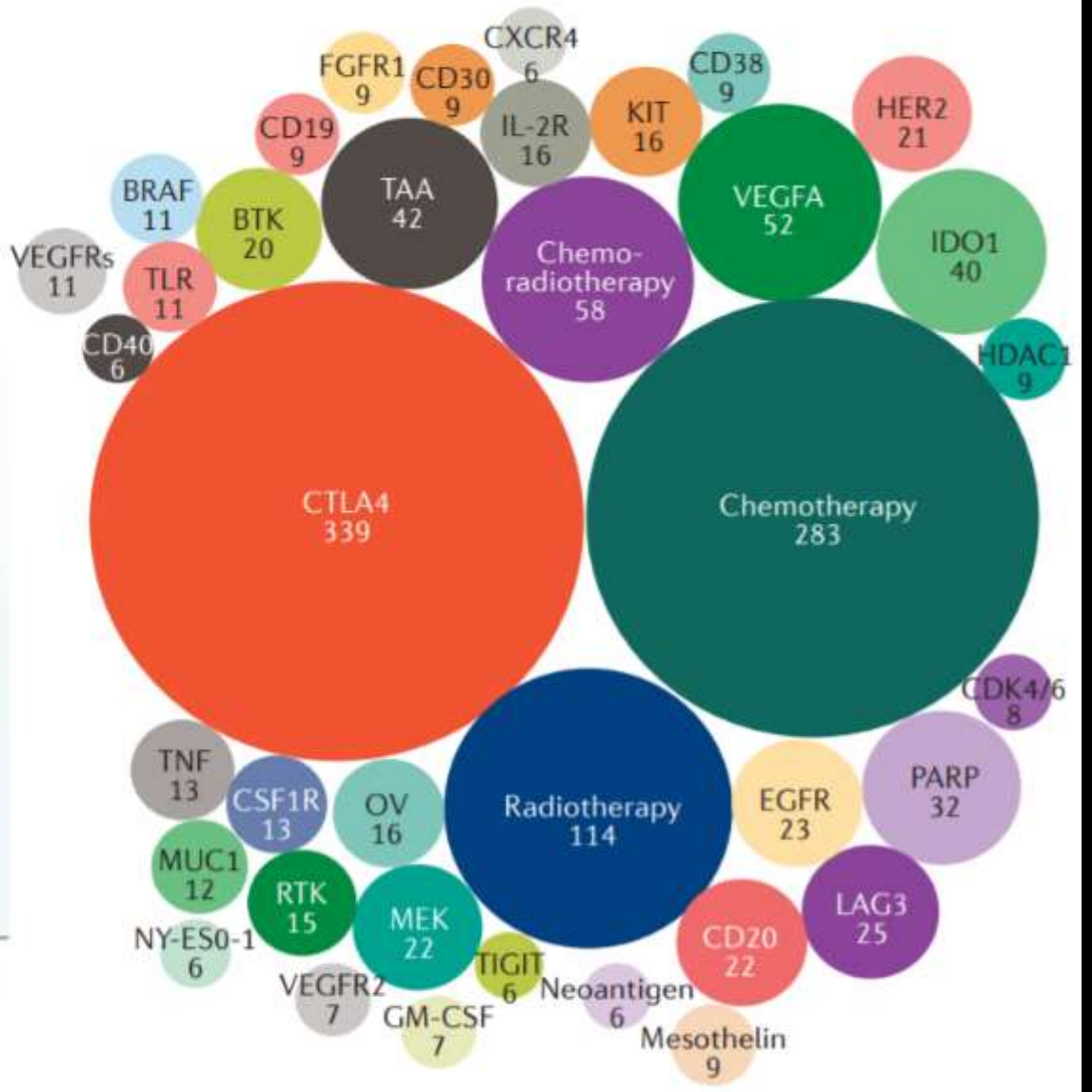
urgent clinical and economic need for multi-parameter immunophenotyping

to reliably predict responder vs non-responder patients and toxicity risk

The Clinical Trial Landscape for PD-1/PDL-1 Immune Checkpoint Inhibitors (2018)

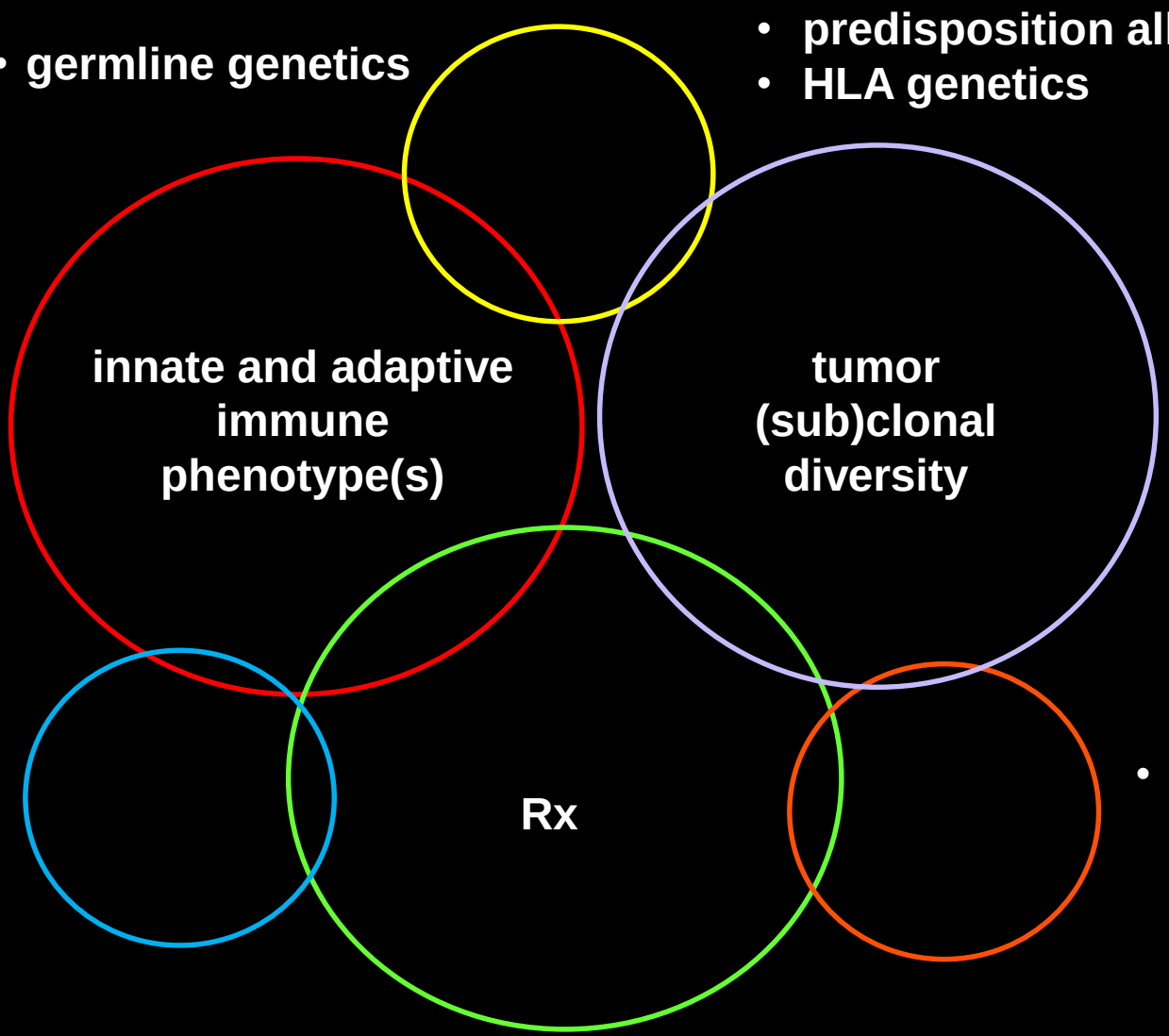
2250 trials; 1716 combination Rx; 240 Rx targets





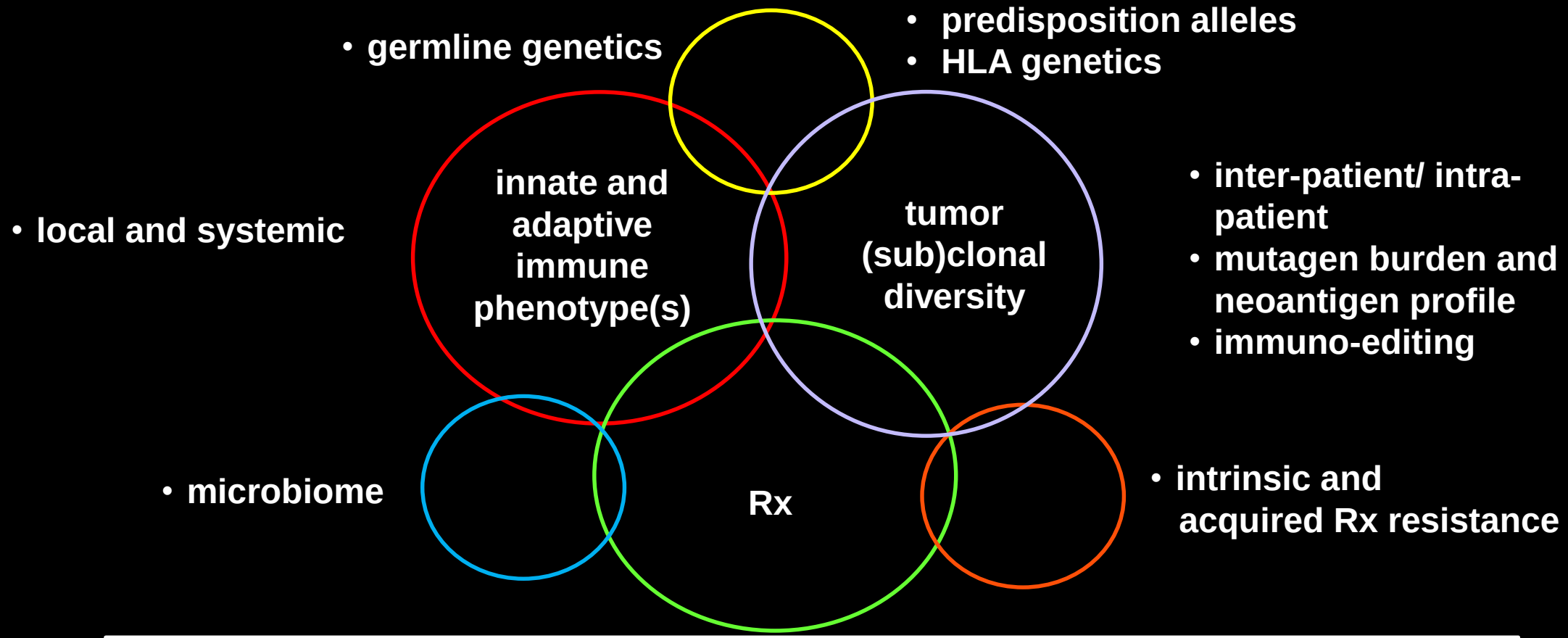
Adapted from: J. Tang et al. (2018) Nature Reviews Drug Disc. 17, 854-55 10.1038/nrd.2018.210

Cancer as a Complex Adaptive System



- germline genetics
- predisposition alleles
- HLA genetics
- local and systemic
- inter-patient/ intra-patient
- mutagen burden and neoantigen profile
- immuno-editing
- microbiome
- intrinsic and acquired Rx resistance

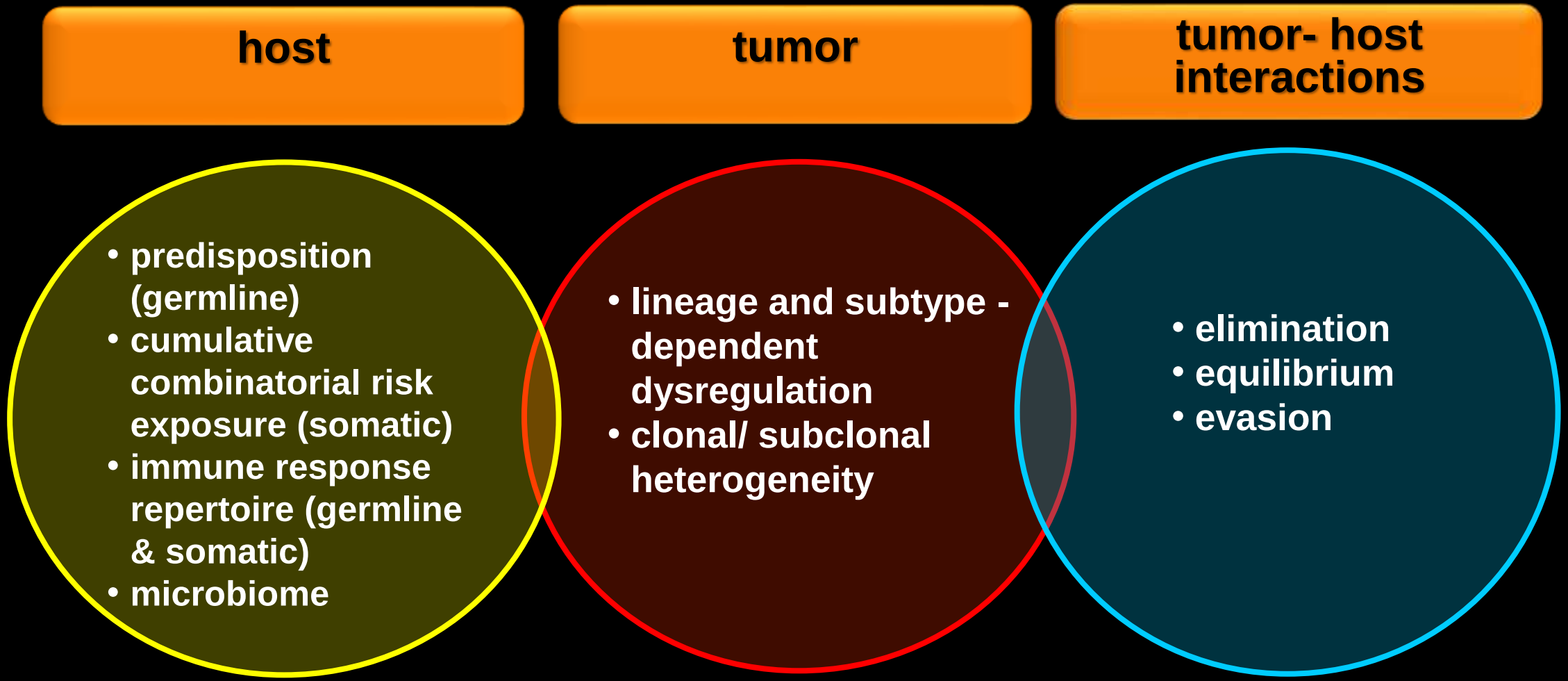
Cancer as a Complex Adaptive System



ill-defined systemic factors affecting disease risk, progression and Rx responses

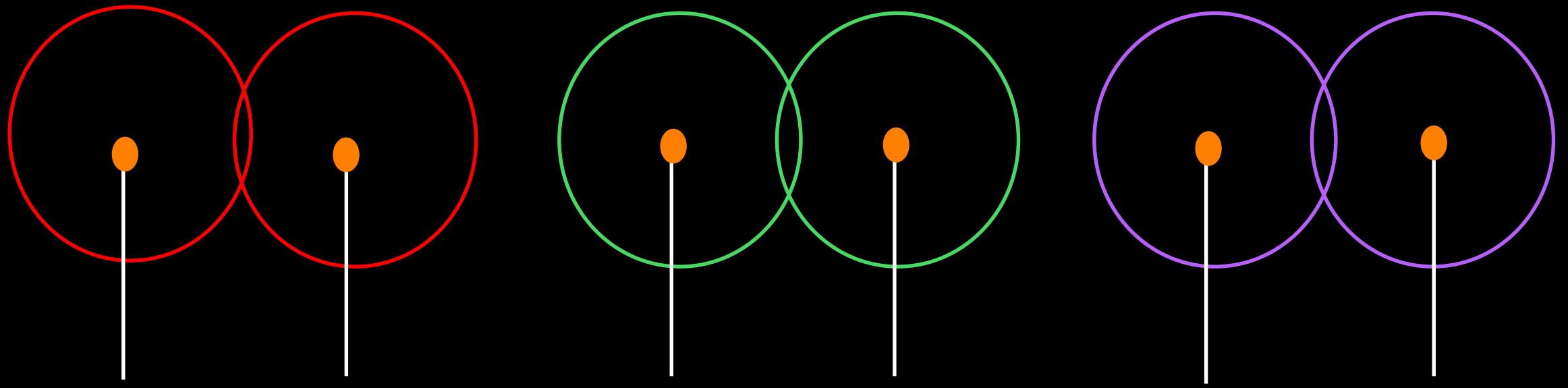
- age
- gender
- ethnicity
- environmental risk factors/lifestyle
- adiposity
- comorbidities
- microbiome
- chronic subclinical inflammation
- selection pressure of prior Rx regimen(s)
- variations in clinical practice: AMCs vs community practices

Cancer: The Interplay Between Multiple Complex Adaptive Systems



spatial and temporal dynamic range
• molecular networks to the whole organism • preclinical events and clinical phase events

The Discovery, Development and Validation of Predictive and Prognostic Biomarkers in Immunotherapy: A Complex Multi-step, Multi-dimensional Process



specimen(s) and sampling frequency

analytes and analytical platforms

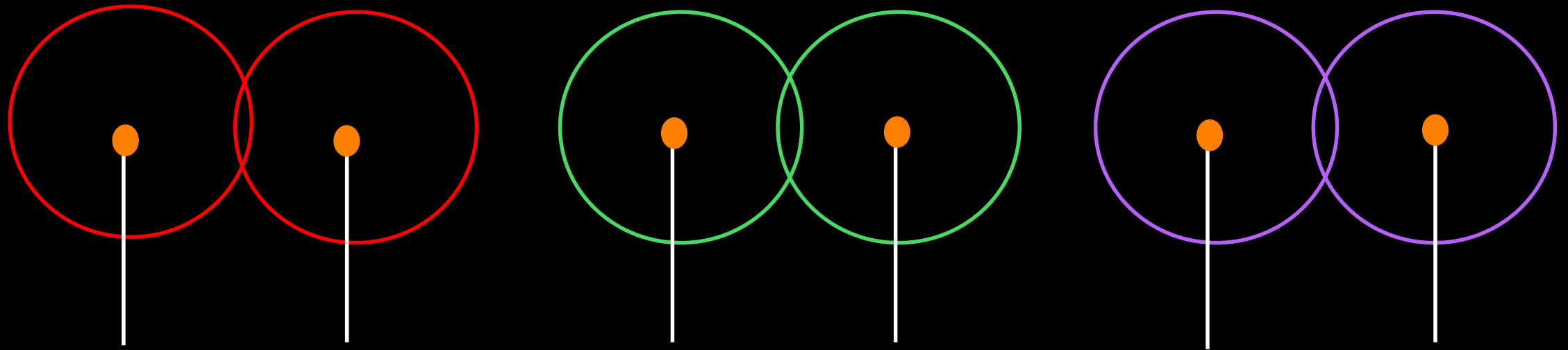
standards for pre-analytical and analytical validation

clinical validation and utility

regulation

reimbursement, pricing and value-based contracting

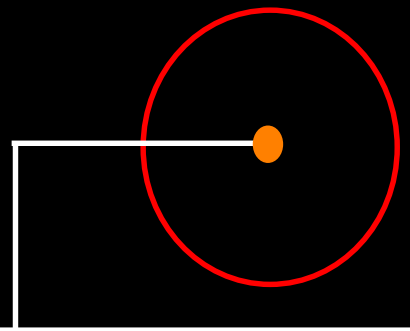
The Discovery, Development and Validation of Predictive and Prognostic Biomarkers in Immunotherapy: A Complex Multi-step, Multi-dimensional Process



- pre-treatment baseline and longitudinal Rx response profiling, AE and HP risk
- concordance of liquid biopsies with intratumoral microenvironment
- standards for clinical staging: ORR, PFS, RFS, OS, AEs, HP
- effect of disease co-morbidities and prior Rx regimen(s)
- cost-effectiveness and value-based pricing

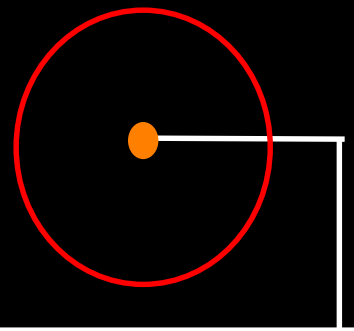
Identification and Validation of Predictive and Prognostic Biomarkers in Immunotherapy

specimen(s) and sampling frequency



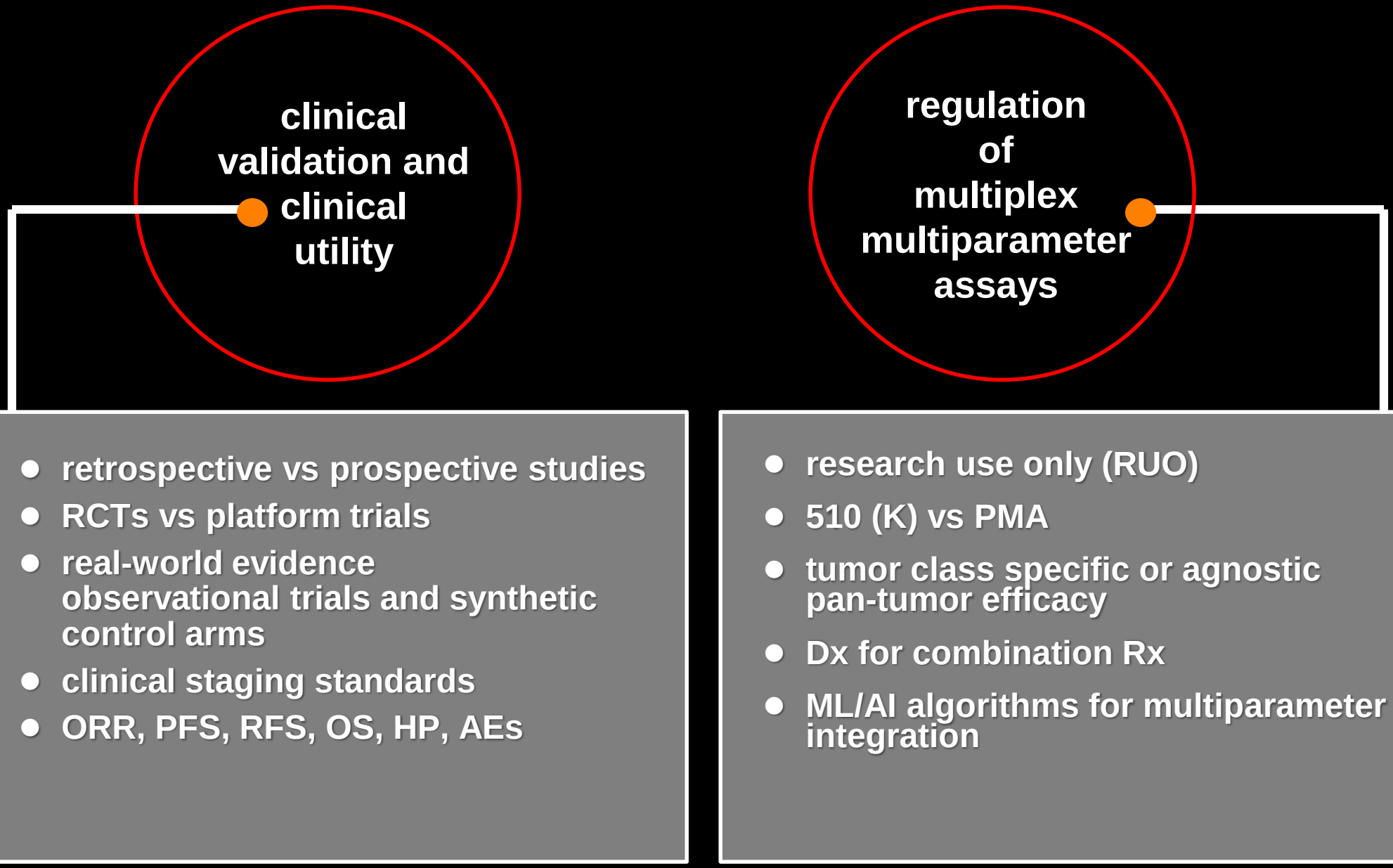
- tissue, body fluids
- bulk versus single cell analysis
- static single biopsy sample versus serial sampling
- germline and somatic variants
- continuous versus discrete biomarker expression dynamic ranges
- laser dissection capture
- frozen/FFPE

analytes and analytical platform standards

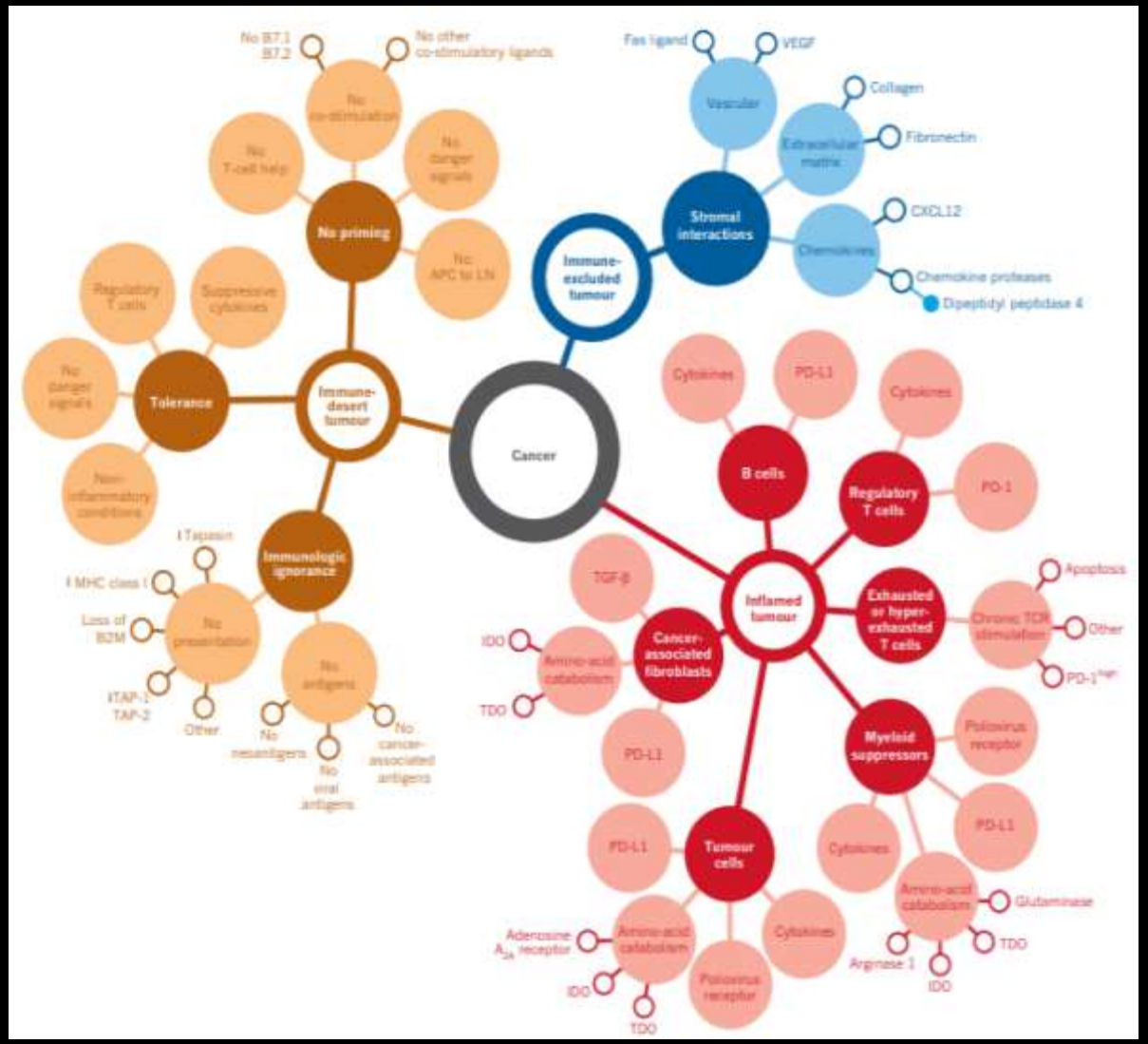


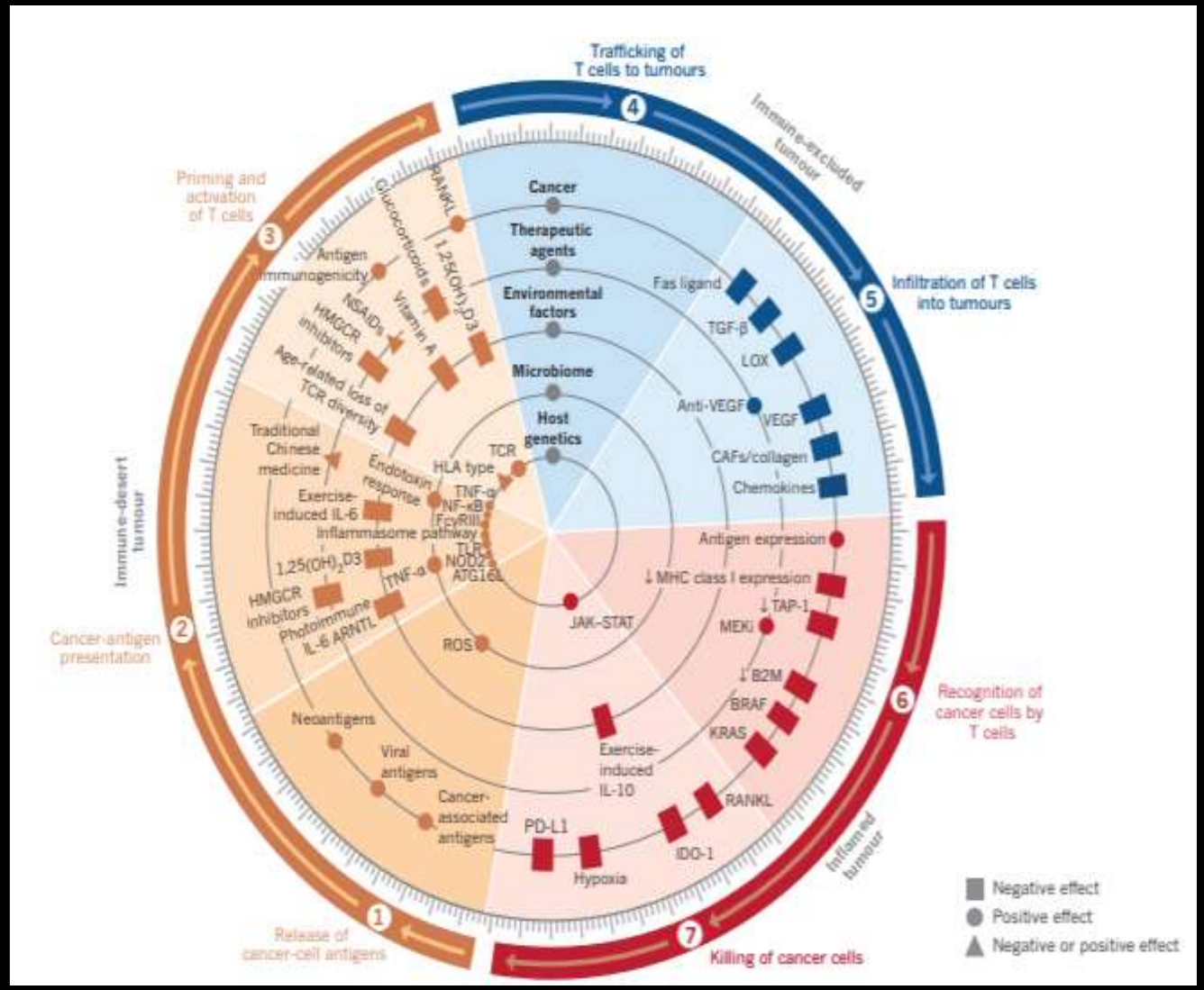
- multiOmics
- cyTOF
- multiplex IHC digital imaging and spatial interaction patterns
- exosomes/EVs
- patient derived organoids and xenografts
- radiomics
- statistically-powered ‘N’

The Discovery, Development and Validation of Predictive and Prognostic Biomarkers in Immunotherapy



Cancer-Immune Phenotypes



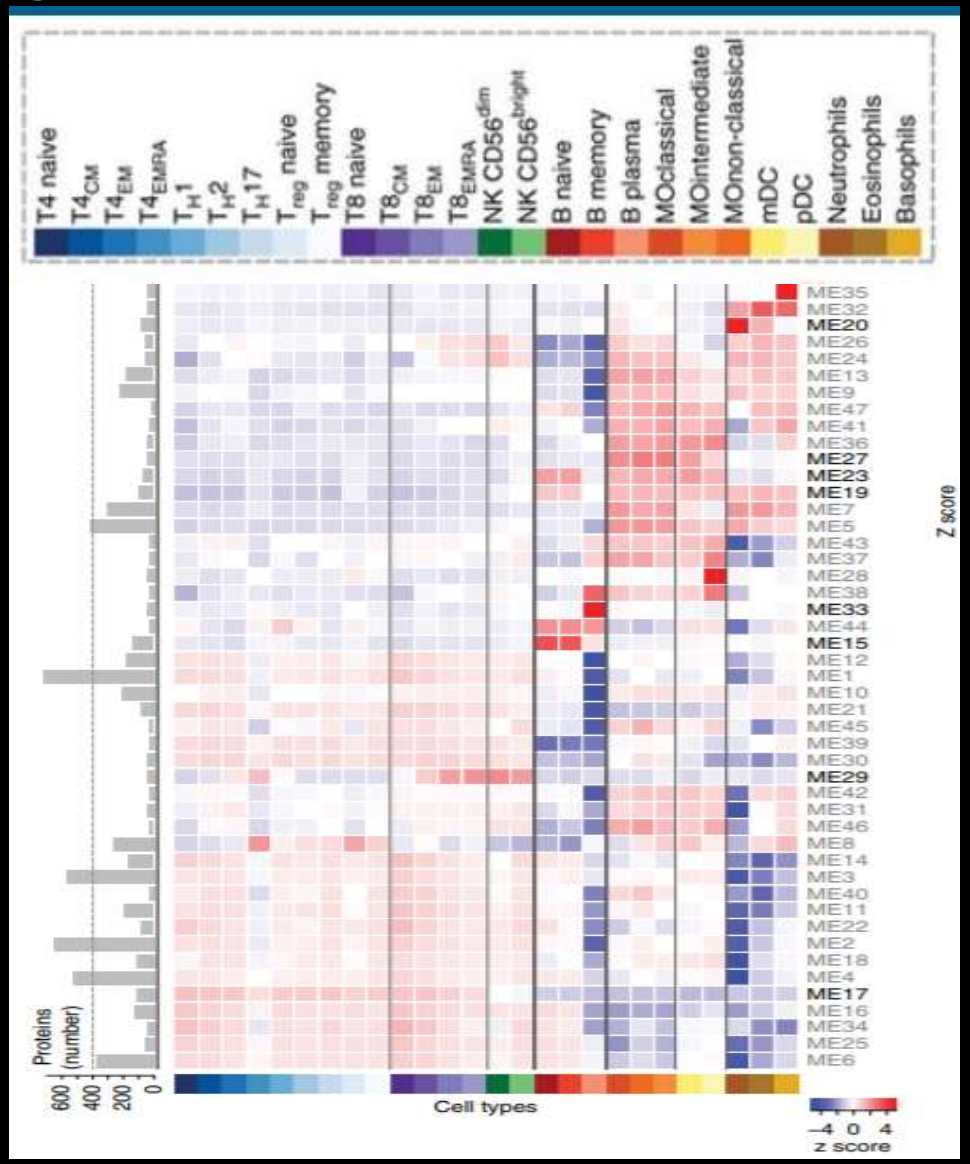


From: D. S. Chen and I. Mellman (2017) Nature 541,34

System-Level Characterization of Tumor-Immune Interaction Networks

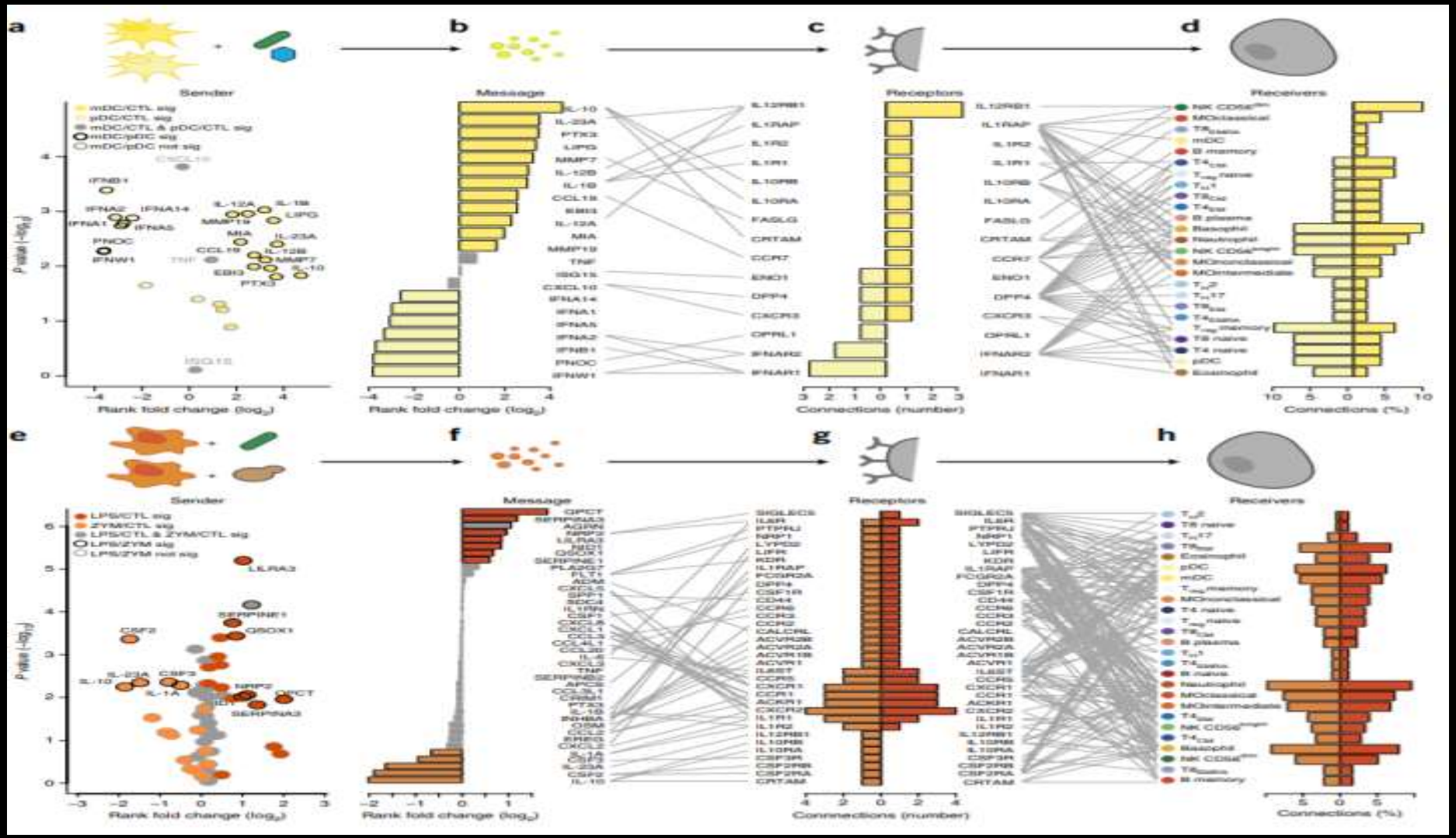
Intractable to Reductionist Methods

Classification of 47 Modules Defined by Weighted Gene Cluster Network Analysis in 28 Human Immune Cell Subsets



From: J. C. Rieckmann et al. (2017) Nature Immunol. 18, 583

Cell-Type and Context-Dependent Expression of Secreted Proteins in Activated Myeloid Dendritic Cells



From: J. C. Rieckmann et al. (2017) Nature Immunol. 18, 583

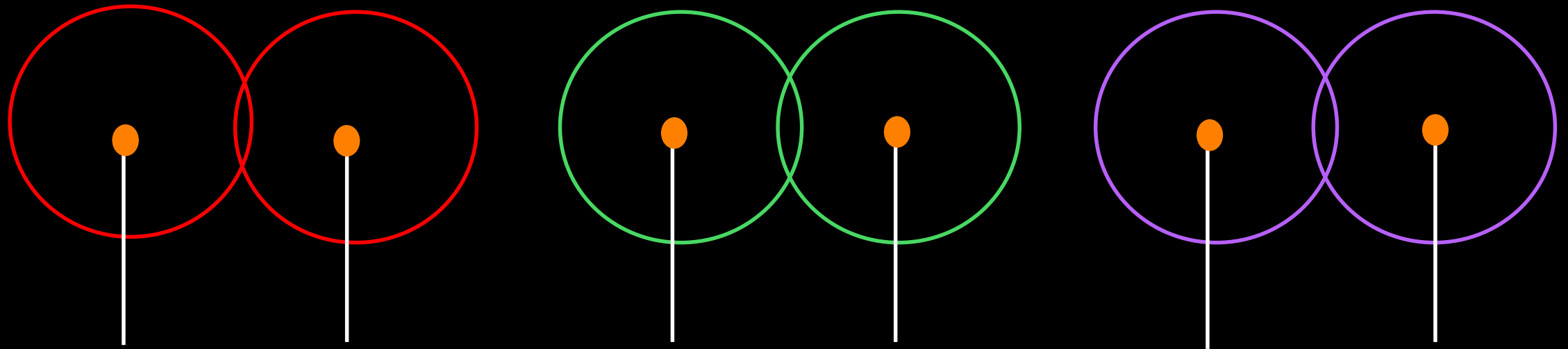
The Discovery, Development and Validation of Predictive and Prognostic Biomarkers in Immunotherapy

- high dimensional phenotyping on an unprecedented scale
  - from multiOmics profiling to stringent clinical annotation
- daunting level of theoretical ‘large N’ combinatorial interactions
  - tumor (sub)clonal heterogeneity, diversity of immune cell subsets, signaling molecules and intracellular pathways
- different dynamic ranges for different analytes/feature sets
- continuous versus discrete signals
- linear and non-linear effects in input:output interactions an d biological outcomes
- inter-dependent and independent variables affecting the same phenotype
- need for very large analytical cohorts for multiparameter analysis

The Discovery, Development and Validation of Predictive and Prognostic Biomarkers in Immunotherapy

- massive data
  - design of experimental protocols to integrate diverse datasets
  - data standards and format for data exchange and meta- analysis
- new computational ML/AI algorithms for multiparameter feature extraction and building classifiers
- new regulatory paradigms for Dx-Algo validation and constant refinement (V1, 2…n)

The Discovery, Development and Validation of Predictive and Prognostic Biomarkers in Immunotherapy: A Complex Multi-step, Multi-dimensional Process



The Curse of Dimensionality (n < p)
• number of independent observation (n) is vastly smaller than number of potential features in the raw data sets (p) and omnipresent risk of overfitting

A Broad Classification of Tumor-Immune Microenvironment (TME)

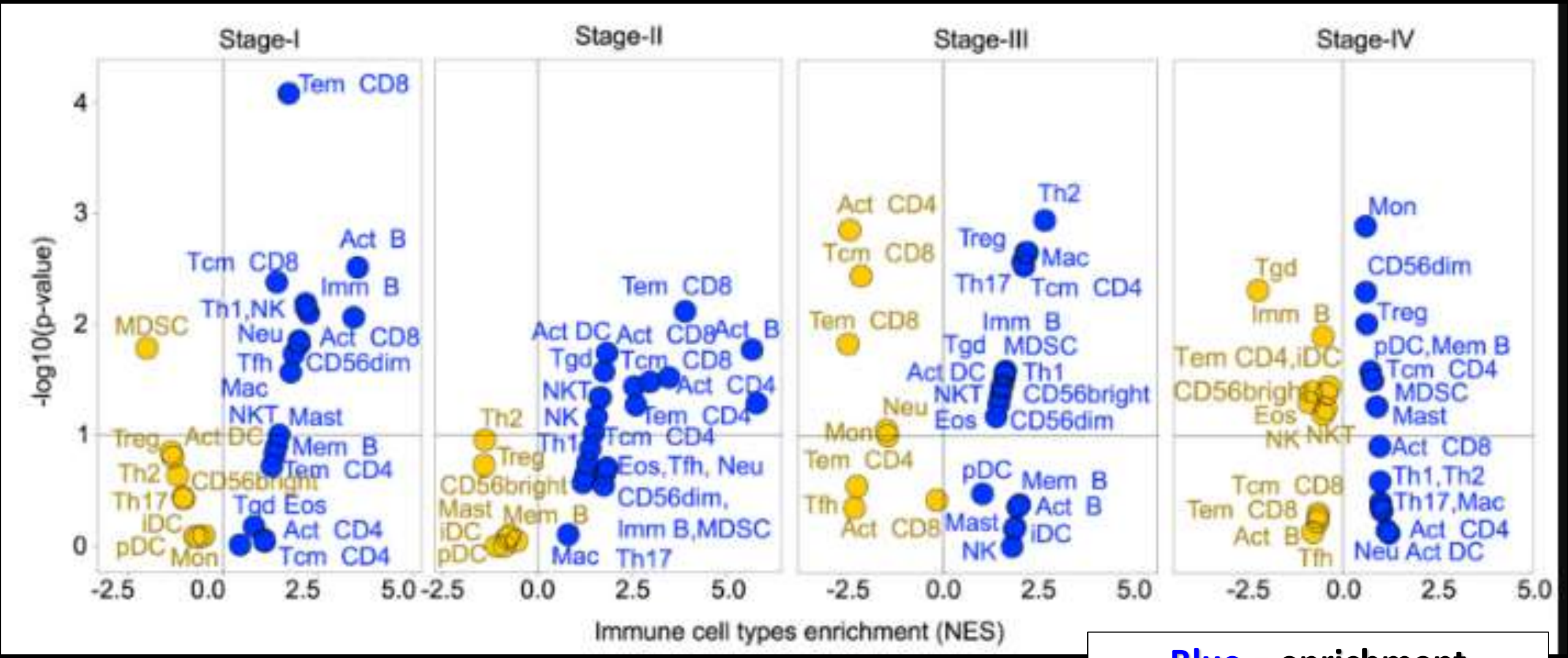
• high TMB • high T cell-inflamed signature	• high TMB • low T cell-inflamed signature
• low TMB • high T cell-inflamed signature	• low TMB • low T cell-inflamed signature

Tumor Immunophenotypes Associated With Responsiveness to Immune Checkpoint Blockade

"Hot", "Inflamed", "Immunogenic"

- high tumor mutation burden
- high tumor-infiltrating $CD8^+$ cytotoxic cells
- activation of tissue-resident T cells (Tres)
- long lived memory T cells (Tem)
- high Th1 and T17 helper cells
- CD21+DCs
- high expression of Th1 stimulating cytokines
  - CCL2,3,4,5, CSC29, CXCd10
- higher expression of TIL checkpoint receptors
  - PD-1, PD-L1, CTLA-4, LAG3
- M1 phenotype tumor-associated macrophages (TAM)
- low Tregs, MDSCs
- low TGF-β

Shifts of Intratumoral Immune Cell Populations to Immunosuppressive Phenotypes with Tumor Progression



P. Charoentong et al. (2017) Cell Reports 18, 248

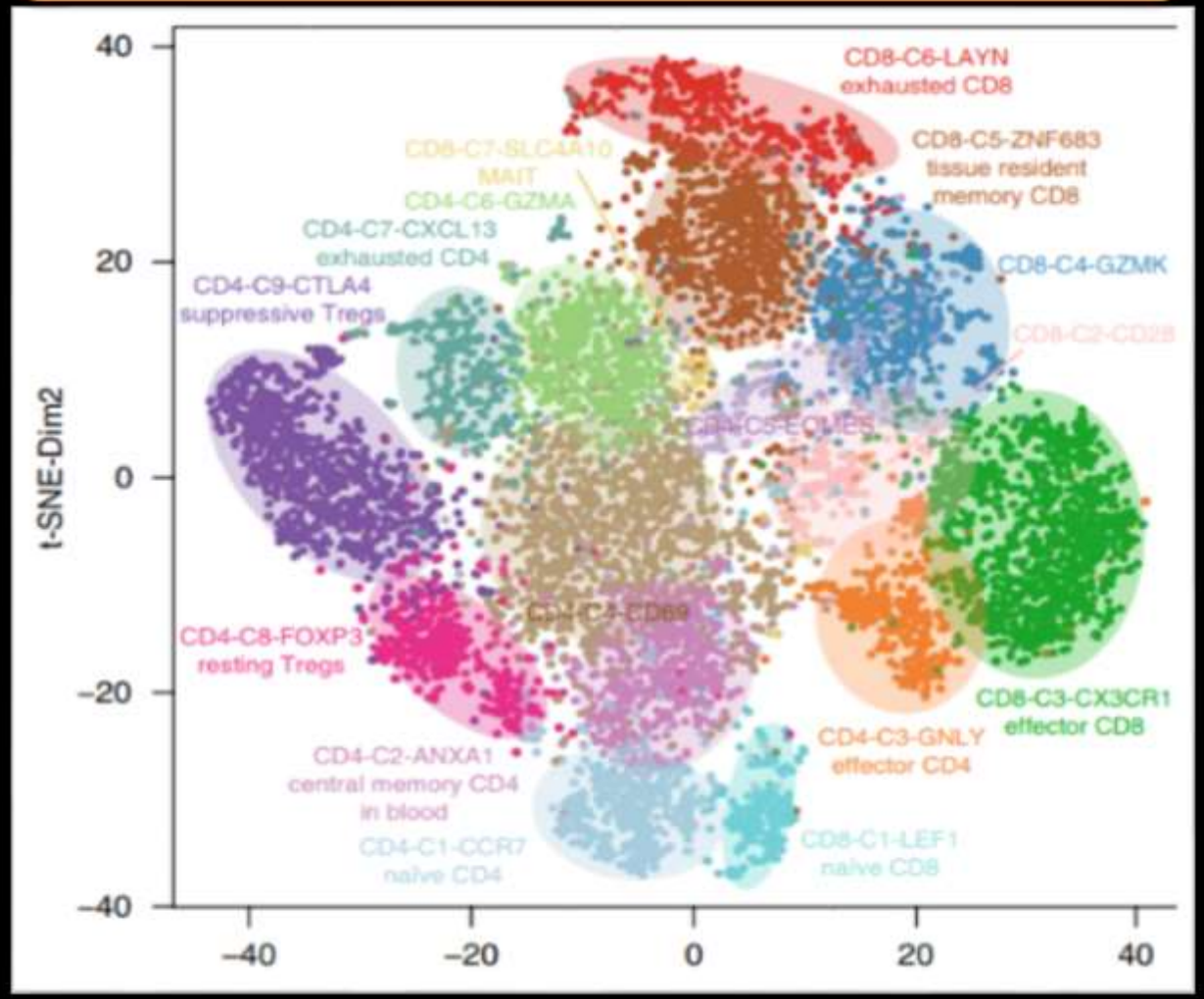
Blue = enrichment

Yellow = depletion

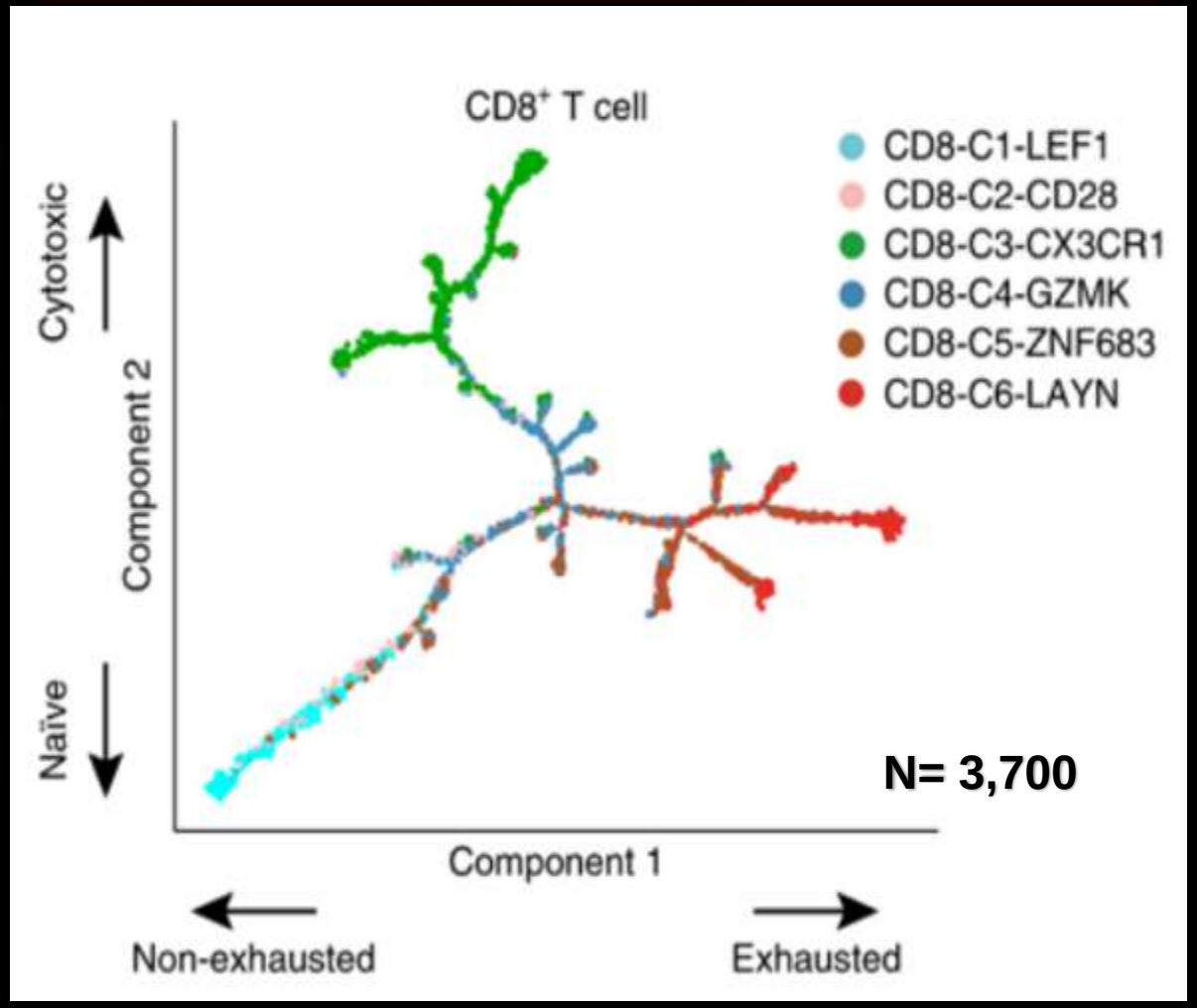
Understanding the (Pre) Exhaustion T Cell Phenotypes Induced by Upregulation of Immune Checkpoint Molecules and Chronic TCR Stimulation

Identification of T Cell ‘State Spaces’ and Responsiveness to Reinvigoration by ICB (and other I/O Rx)

t-SNE Clusters (7) of Single Cell Analysis and Clustering of T Cell Subsets in Cancer



Single Cell Analysis of CD8+ Cell State Transitions

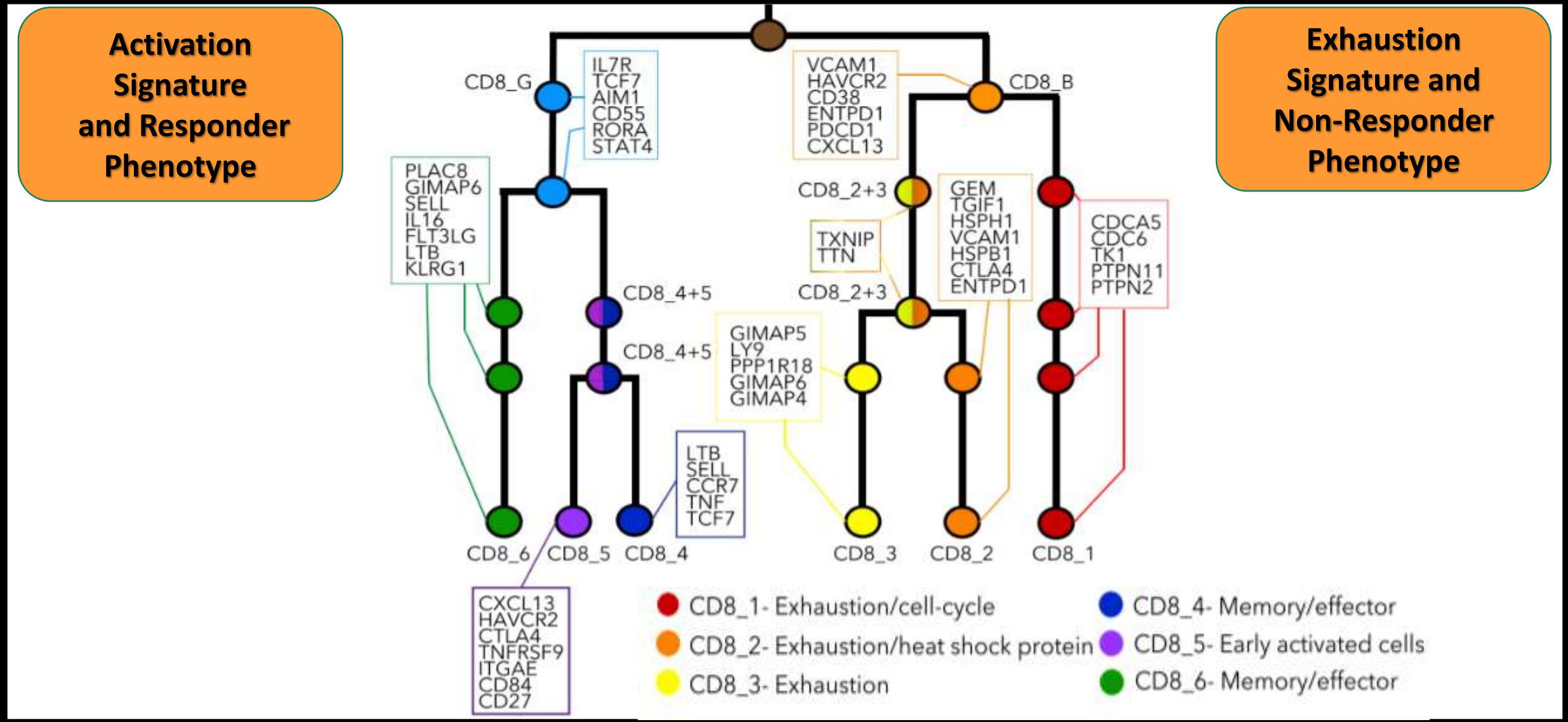


Adapted from X. Guo et al. (2018) Nat. Med. 24, 479

CD8+ T Cell State Heterogeneity and Association with Clinical Response in Melanoma

Activation Signature and Responder Phenotype

Exhaustion Signature and Non-Responder Phenotype

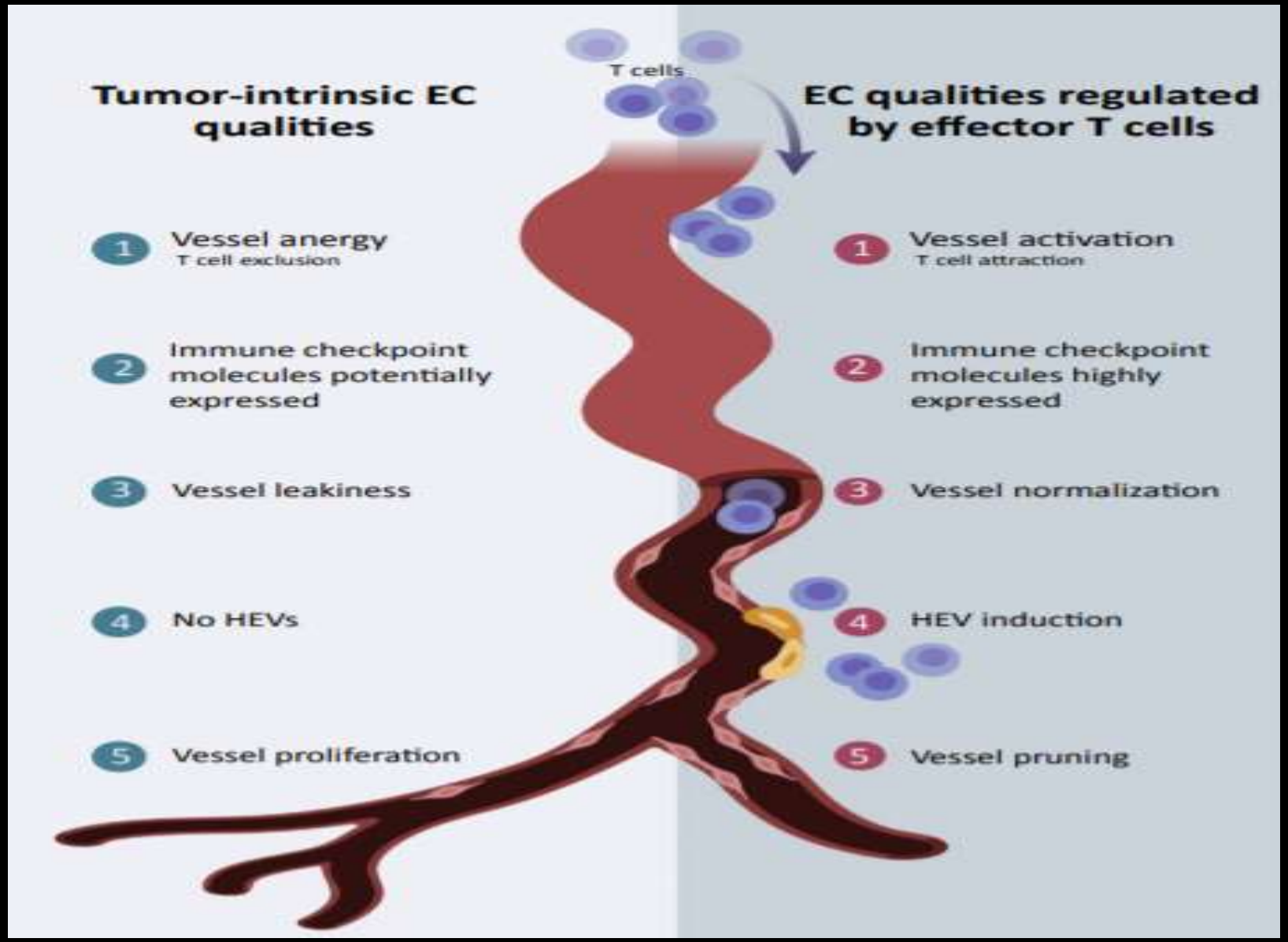


Adapted from: M. Sade-Feldman et al. (2018) Cell 175, 998-1013

Mechanisms of T Cell Exclusion from Tumor Infiltration

The Vascular: Immune Checkpoint as a Therapeutic Target?

The T Cell-Vascular Interface: Vessel Architecture and T Cell Extravasation



From: A. Johansson-Percival et al. (2018) Trends in Immunol. 39, 801 https://doi.org/10.1016/j.it.2018.08.001

The Vascular: Immune Checkpoint: A New Therapeutic Target?

- tumor-mediated exclusion of T cell extravasation and intratumoral infiltration
- inhibition of T cell adhesion and rolling on activated HEV
- PAK4 upregulation and β-catenin (SITC 2018 Abstract 039)
- GDF-15 upregulation (growth and differentiation factor 15)
  - impaired activation of lFA-1 on T cells and reduced endothelial binding (SITC 2018 Abstract 041)
- melanoma CDK4 upregulation signature associated with exclusion but role in T cell egress unknown

From: L. Jerby-Arnon et al. (2018) Cell 175

Tumor Immunophenotypes Associated With Non-Responsiveness to Immune Checkpoint Blockade

"Cold": "Non-Inflamed", "Non-Immunogenic", "Immune Desert"

- low mutational and neoantigen burdens
- low $CD8^+$ effector cells
- high Tregs and MDSCs, low Th1
- immunoediting and loss/down-regulation of neoantigens
- impaired antigen presentation
  - loss/downregulation of MHC
  - JAK 1/2 and β2 microglobin mutations in MHC1
- increased levels of immunosuppressive cytokines
  - PTEN loss and increased CCL2, VEGF and reduced T cell infiltration
  - catenin/Wnt mutations and reduced CCL4 chemokine production and dendritic cell recruitment
- CCR2/CCL2 and M2 phenotype TAMs
- IPRES (innate PD-1 resistance) gene signature
  - immunosuppressive cytokines, EMT-TFs and pro-angiogenic factors

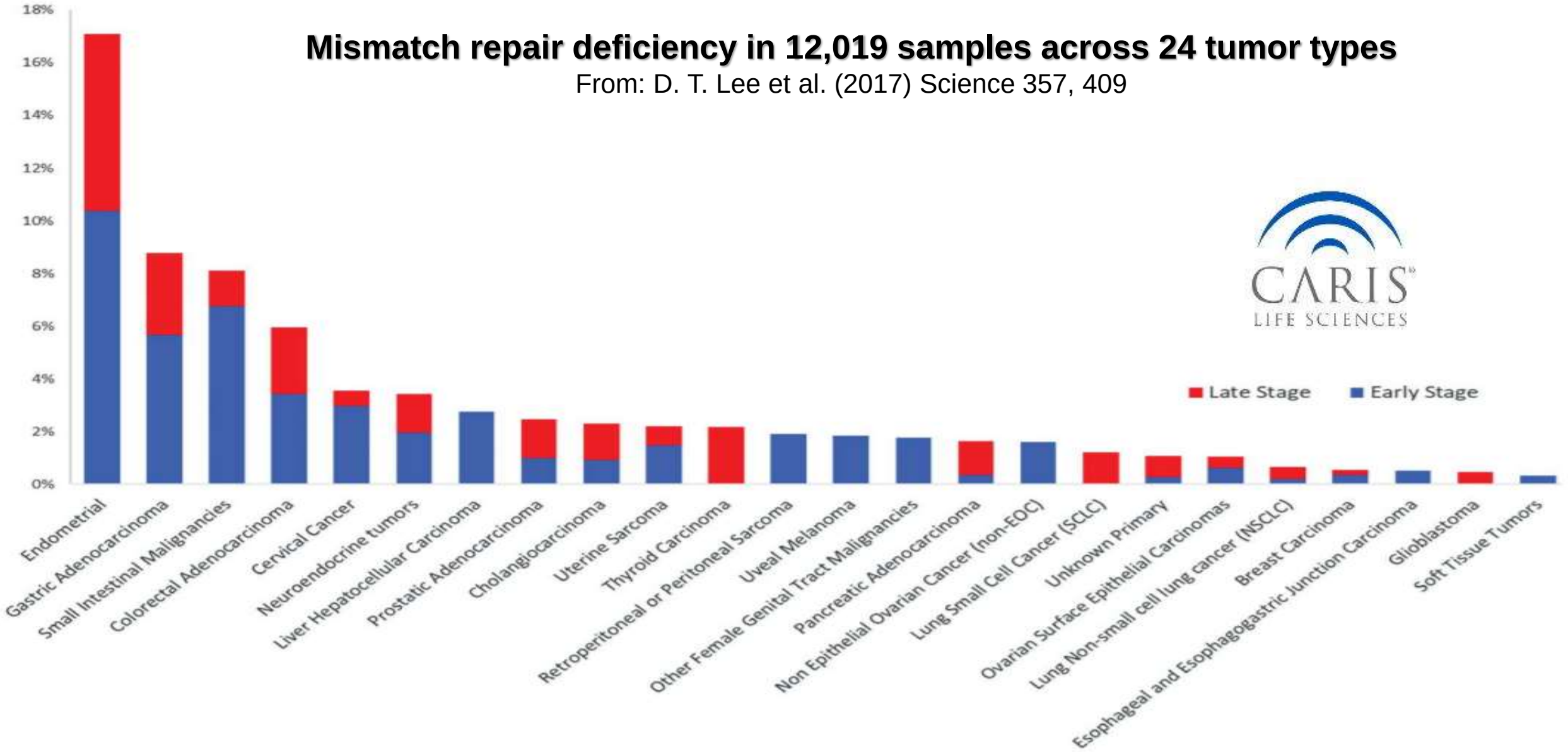
PDL-1 Expression as a Predictive Biomarker for Anti-PD-1 and Anti-PDL-1 Therapy

PDL-1 Expression as a Predictor of ICB Response

- imperfect as stand alone response predictor
- multiple studies correlating PDL-1 expression on tumor cells with response to ICB but others detect no association
- patients with low to no detectable PDL-1 can experience durable clinical benefit
- heterogeneity in cell type expression
  - TILs versus tumor cells
- non-standardized detection assays and cut-off points for IHC positivity and staining intensity

Tumor Mutation Burden (TMB), DNA Mismatch Repair Deficiency (MMRd), Microsatellite Instability (MSI-H), Neoantigen Burden and Response to ICB

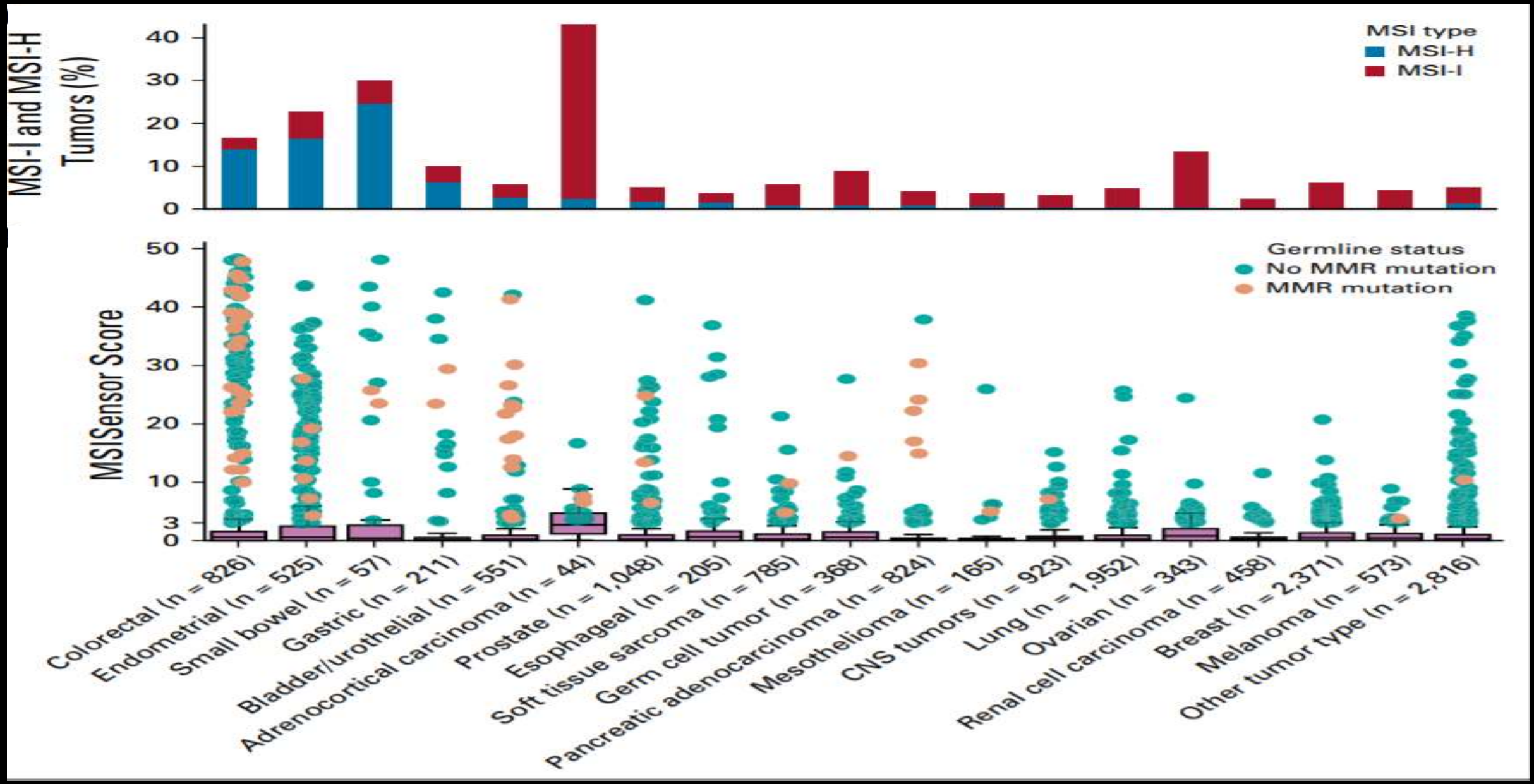
Mismatch Repair Deficiency Predicts Response of Solid Tumors to PD-1 Blockade



Cancer Phenotype Agnostic Profiling for Microsatellite Instability (MSI) and DNA Mismatch Repair Deficiency (MMRd)

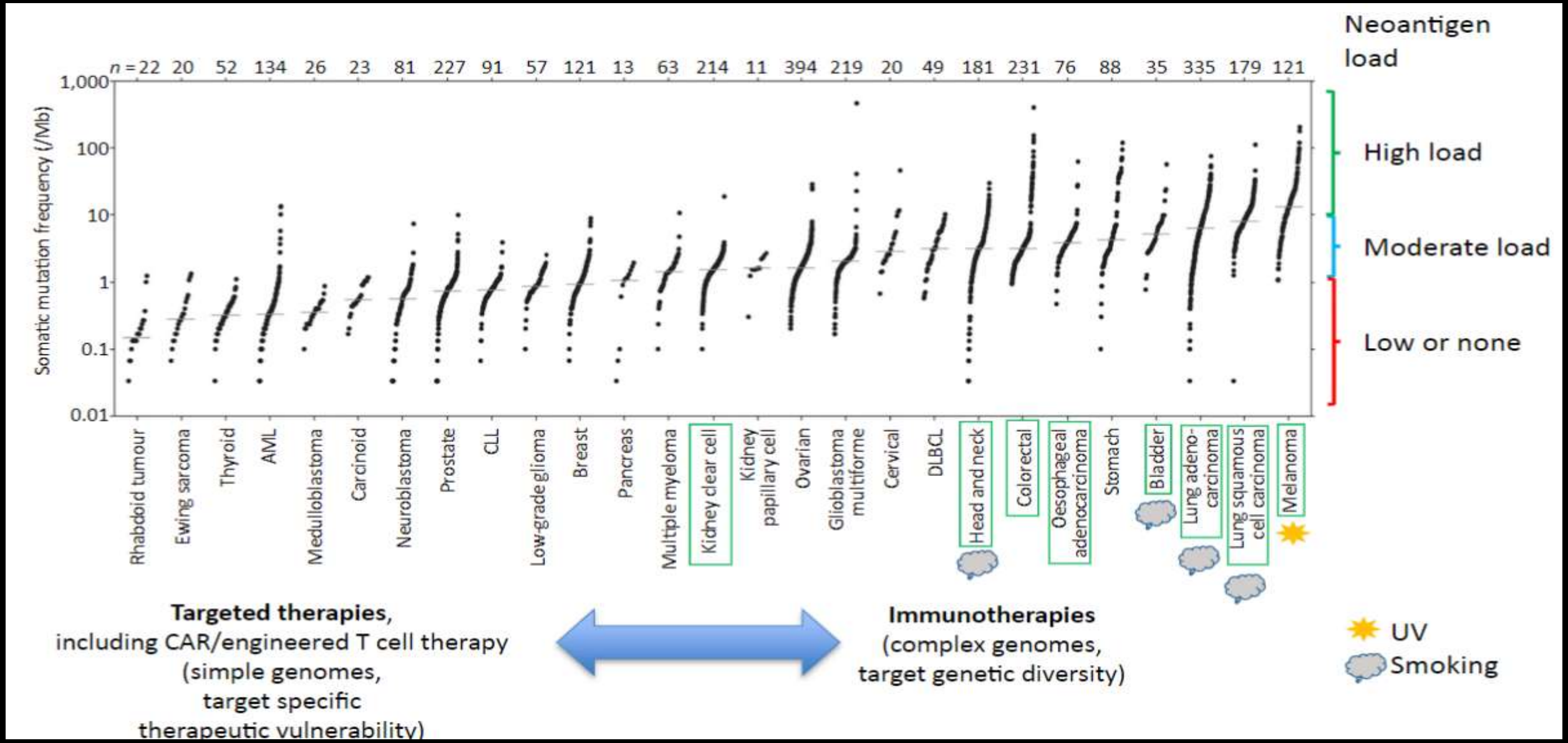
- MSI-high (MSI-H) as lineage agnostic predictive marker for anti-PD-1 immunotherapy
  - FDA approval
- Lynch Syndrome (LS): germline MMRd due to mutations in MLH1, MSH2, MSH6, PMS3, EPCAM
- historical recognition of LS germline MMRd for predisposition to CRC and endometrial cancer
- LS phenotype higher prevalence in other malignancies than previously recognized
  - A. Latham et al. (2018) J. Clin. Oncol. 286, 37

Distribution of MSI and Germline MMRd Mutation Across Cancer Types (N=15,045)



From: A. Latham et al. (2018) J. Clin. Oncol. 286, 37 https://doi.org/10. 1200/JCO.18.00283

TMB, Neoantigen Expression and I/O Rx Efficacy



From: C-H Lee et al. (2018) Trends in Immunol. 39, 536
https://doi.org/10.1016/j.it.2018.04.005

Tumor Mutation Burden (TMB) and ICB Response

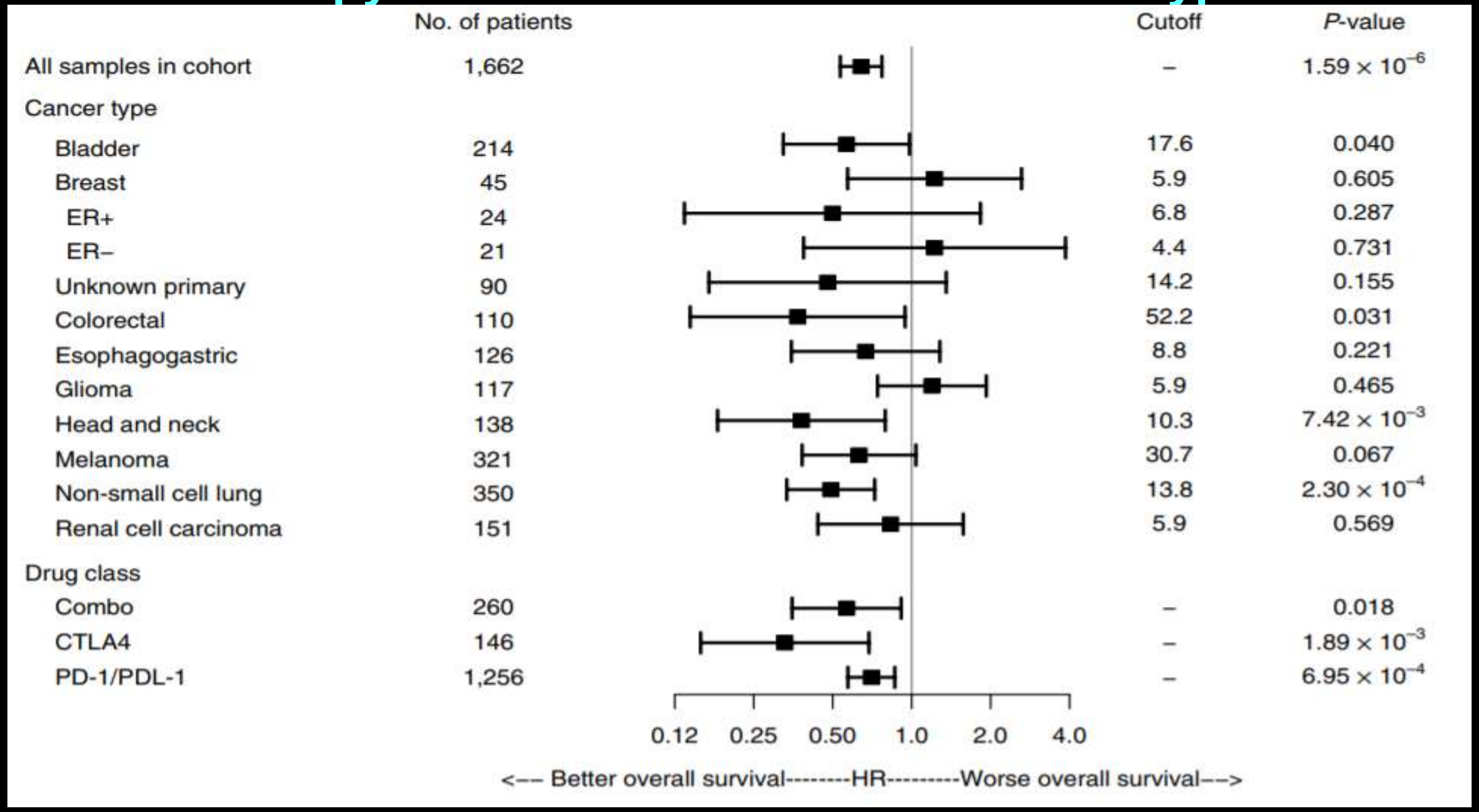
- positive pan-cancer correlation with PFS across 27 tumors
- outliers
  - Merkel cell carcinoma and RCC higher response than predicted by TMB
  - mismatch repair proficient CRC less responsive than predicted by TMB
- TIL immune infiltration correlates with TMB and/or neoantigen burden
  - correlation for cancers driven by recurrent mutations but not those driven by copy number alterations (breast, pancreas)
  - RCC outlier as highest immune infiltration score despite low TMB
- case by case patient variation within every lineage

FRIENDS of CANCER RESEARCH

Tumor Mutational Burden (TMB)

	Analytical Validation		Clinical Validation
Workflow	Step 1: In silico analysis	Step 2: Empirical analysis	Step 3: Clinical analysis
Samples	Publicly available TCGA data	Cells derived from human tumors	Clinical Samples
Goals	Identify sources of variability between TMB calculated using whole exome sequencing (WES) & various targeted panels used in the clinic	Agree upon creation of a universal reference standard using WES Identify sources of variability after alignment of TMB scores from targeted panels to the reference standard	Conduct a retrospective analysis using patient outcome data to assess the variability around clinically meaningful cut-off values and inform clinical use.
Timeframe	May 2018	Fall 2018	Winter 2018/Spring 2019

Cutpoint for Top 20% TMB Associated with Longer OS with ICB Therapy Varies Across Different Tumor Types



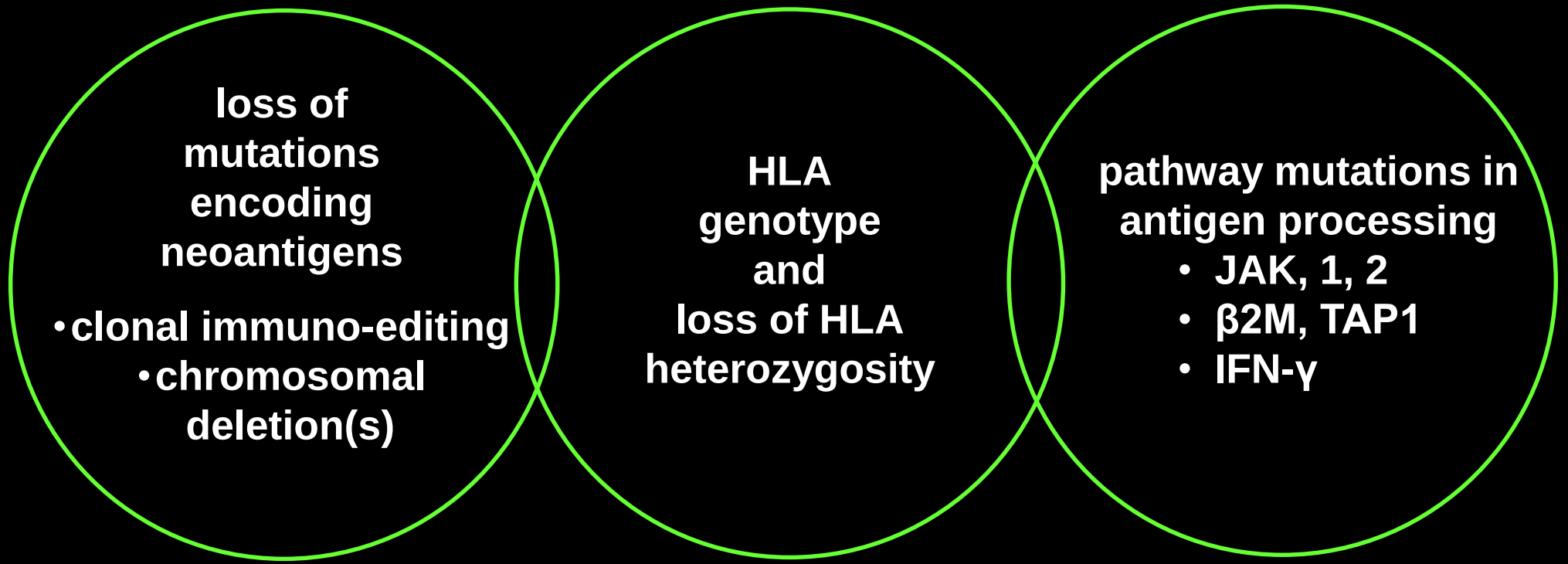
From: R. M. Samstein et al. (2019) Nature Genetics 51, 202

Lineage-Specific TMB Cutoff Scoring

- rank individual patient TMB score as a percentile within overall dynamic range for their tumor class

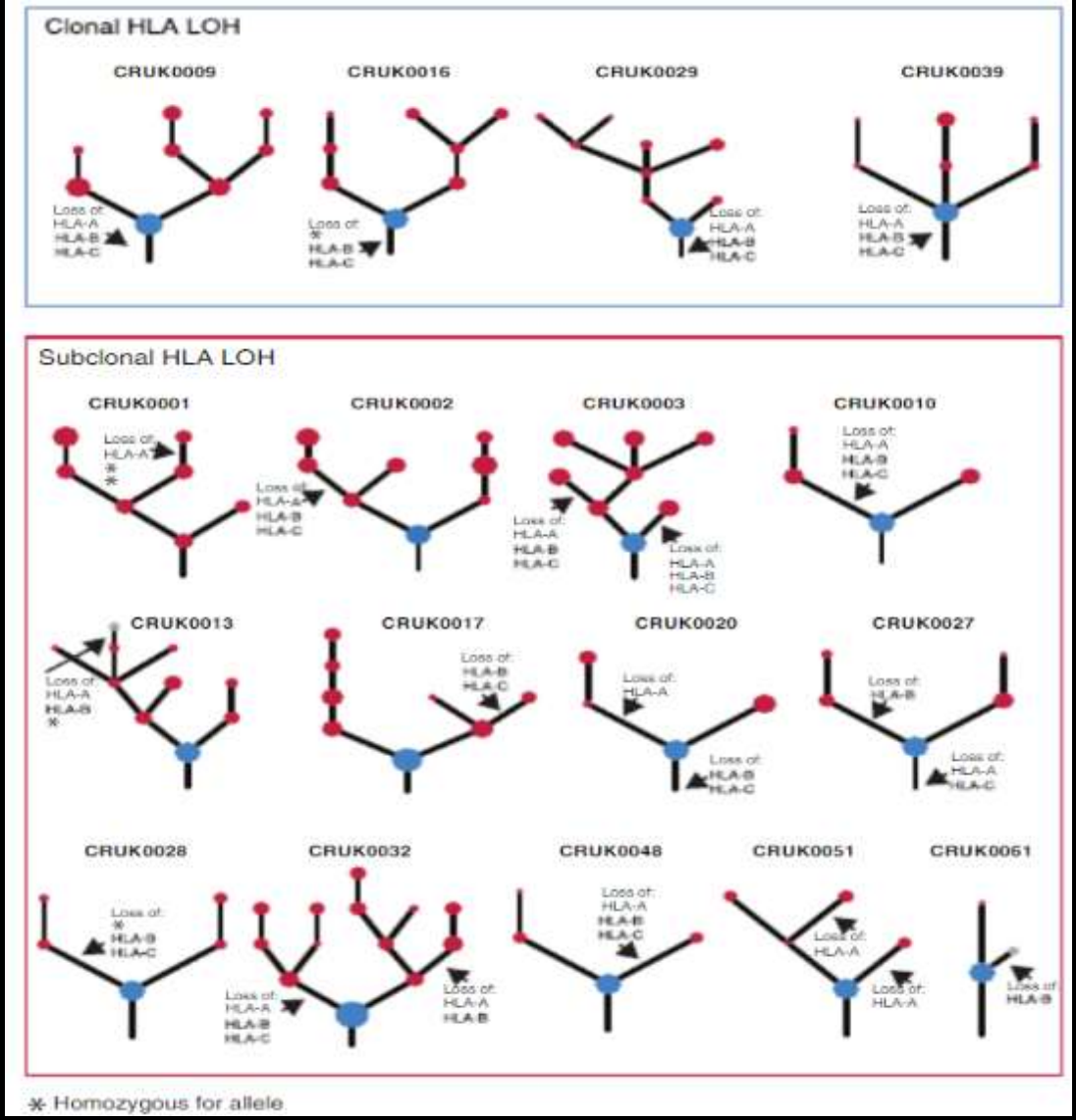
Neoantigen Expression and Detection in Prediction of Responsiveness to Immune Checkpoint Blockade (ICB)

- antigen loss/reduced expression
- impaired immune recognition and antigen processing



intrinsic and acquired resistance to ICB

HLA Loss of Heterozygosity in Lung Adenocarcinoma and Lung Squamous Cell Carcinoma



- HLA loss of heterozygosity and failure to recognize antigenic peptides no longer presented on the lost allele
- enrichment of neoantigens predicted to bind with high affinity to lost vs retained HLA alleles
- higher frequency of LOH in subclones at metastatic sites
  - role of immune microenvironment(s) as a selective force in shaping branched clonal evolution?

From: N. McGranahan et al. (2017) Cell 171, 1259

Epigenetic Marker of anti-PD-1 Response in Stage IV NSCLC*

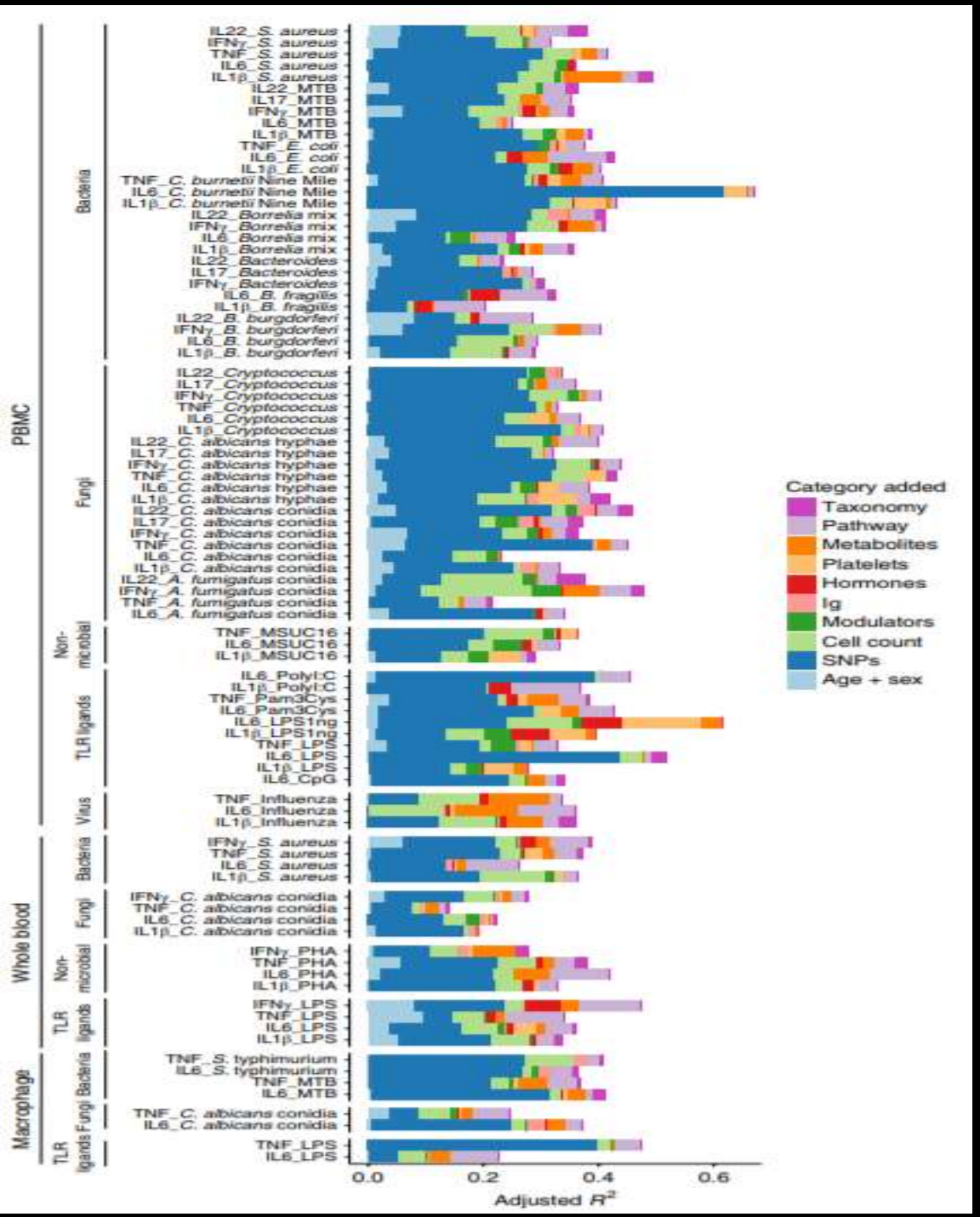
- **unmethylated status of the regulatory T-cell transcriptome factor forkhead box IP (EPIMMUNE positive)**
- **no correlation with clinical benefit in patients not treated with immunotherapy**
- **EPIMMUNE-negative signature in unresponsive tumors enriched in TAMS, neutrophils, CAFs and endothelial cells with senescence phenotype**

*M. Duruisseaux et al. (2018) Lancet Resp. Med. 6, 771

Demethylation Agents for Combination Immunotherapy

- demethylation agents enhance chemokine production by Th cells and T cell trafficking to tumor in preclinical models
  - D. Peng et al. (2015) Nature 527, 249
  - N. Nagarsheth et al. (2016) Cancer Res. 76, 225

Deep Phenotyping and ID of Genetic Contributions to Individual Variation in Cytokine Responses

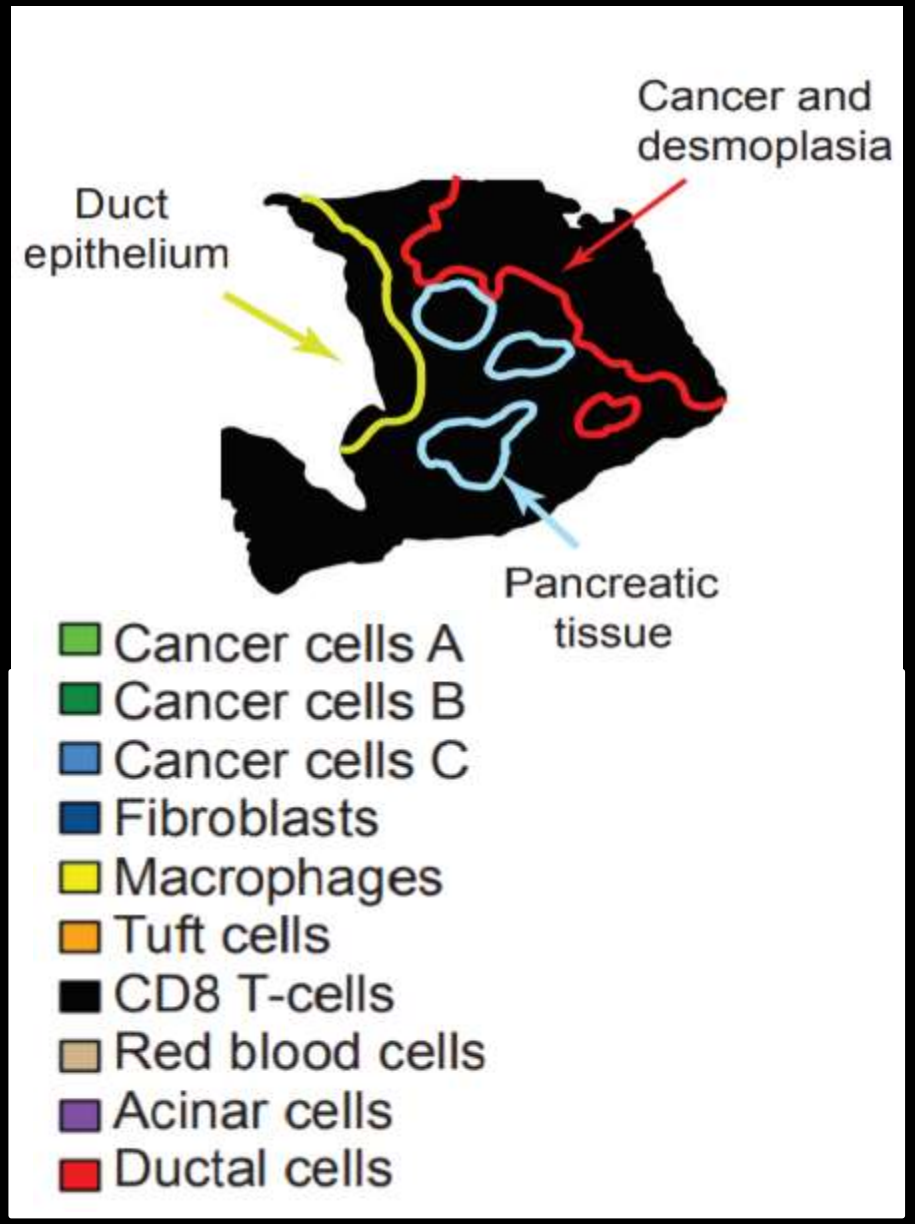


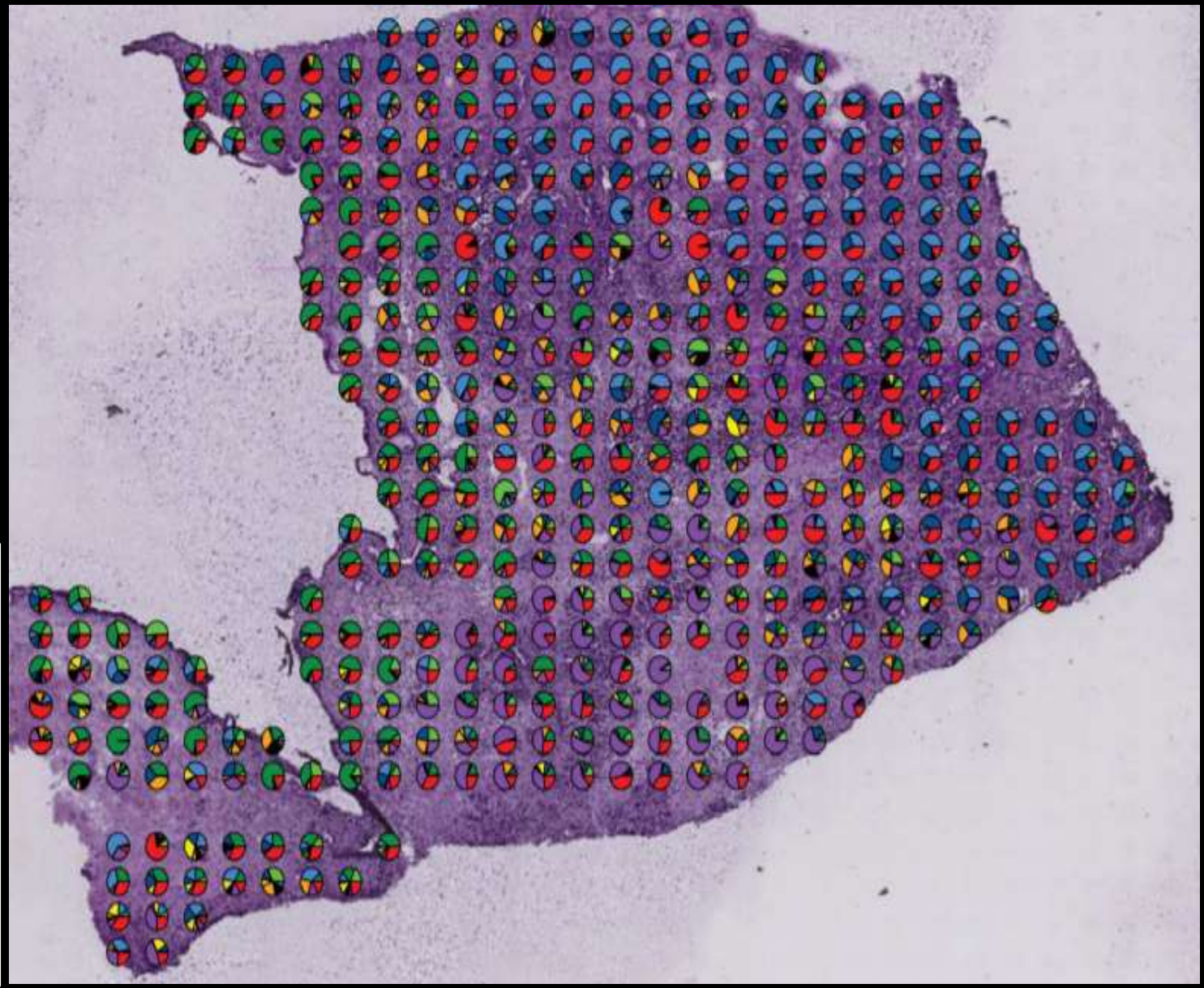
O.B. Bakker et al. (2018) Nature Immunology 19, 776

- 91 cytokine-stimulus pairs in 534 individuals elicited by 20 pathogens
- 70% heritability

do germ line variants in lumphokine/cytokine affect responsiveness to I/O therapy and AE risk (cytokine release syndrome)?

Integration of scRNA Seq and Spatial Transcriptomic in the Analysis of Immune Cell Subsets in Pancreatic Ductal Carcinoma





Adapted from: R. Moncada et al. (2018) bioRxiv254375

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-018-0177-5

Classification and mutation prediction from non–small cell lung cancer histopathology images using deep learning

Nicolas Coudray[1,2,9], Paolo Santiago Ocampo[3,9], Theodore Sakellaropoulos[4], Navneet Narula[3], Matija Snuderl[3], David Fenyö[5,6], Andre L. Moreira[3,7], Narges Razavian[8*] and Aristotelis Tsirigos[1,3*]

- use of Google inception v3 algorithm for analysis of histopathology
  - 10,000 to > 100,000 pixels for 20x to 40x stained images
- robust identification of LUAD and LUSC (AUC of 0.97) comparable to pathologist histopathology classification
- prediction of presence or absence of genes from image data alone
  - EGR, STKII, FAT1, SETBP1, KRA5, TP53

New Digital Pathology Imaging Systems for In Situ Multi-, Super- and Hyperplex Molecular Profiling

- fluorophore-, hapten- or metal-coupled antibodies
- oligonucleotide barcoding
- IF Immunohistochemistry (IF-IHC)
- In Situ Hybridization (ISH)
- Laser Capture Microdissection (LCM)
- Matrix-Assisted Laser Desorption Ionization Imaging Mass Spectrometry (MALDI-IMS)
- Vibrational Spectroscopy
  - two photon absorption fluorescence (TPAF)
  - coherent Raman scattering microscopy (CRS)
  - Fourier Transform Infrared Spectroscopy (FTIR)

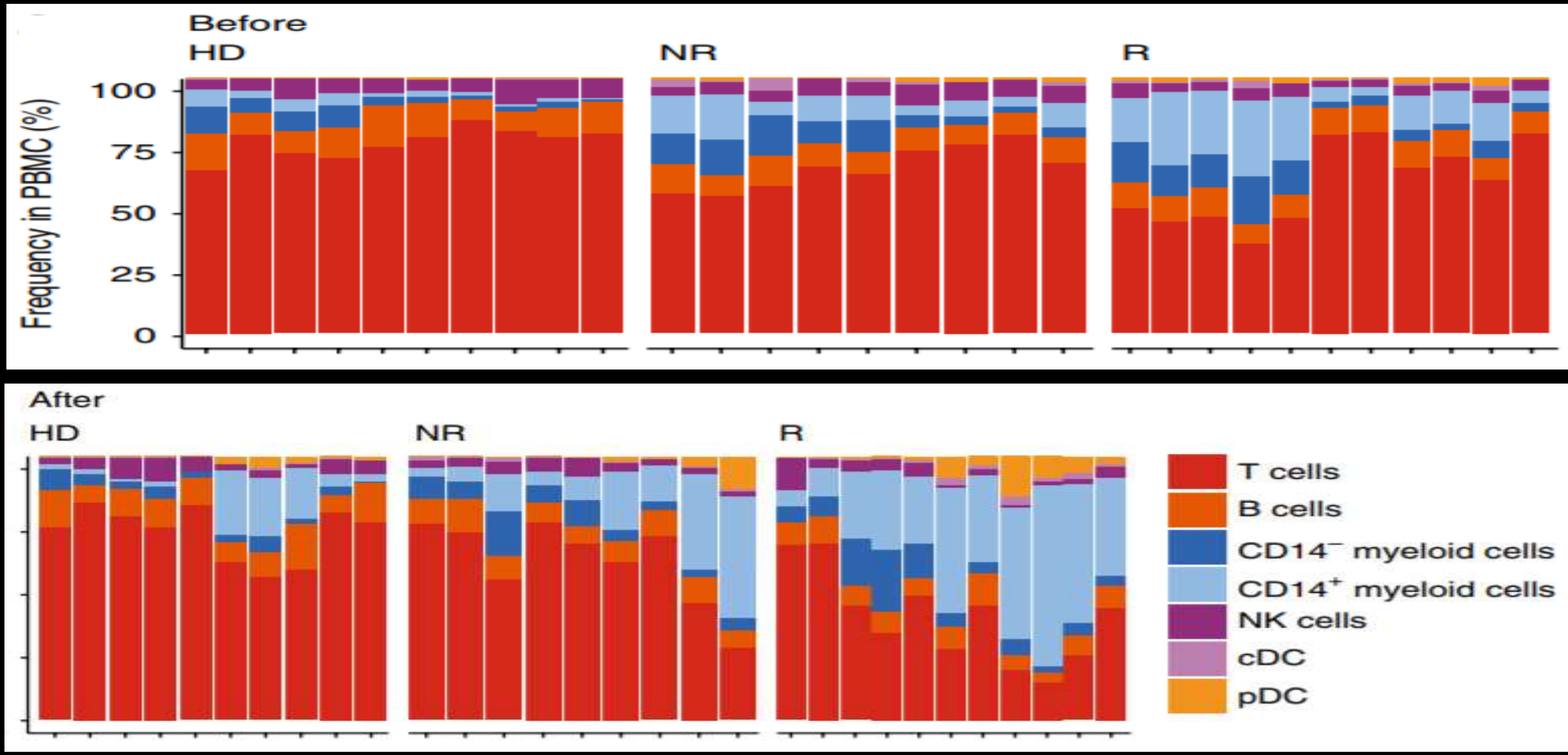
Circulating Biomarkers to Monitor ICB Response Patterns

Circulating Biomarkers Associated With ICB Response*

- TMB high
- ctDNA initial increase with decline to undetectable levels
- loss of PD-L1 positive CTCs ($CD45^{+}$ CK^{+} but need to exclude $CD11b^{+}$ $CD45^{l0}$ CK^{+} myeloid cells as potential false positive)
- initial increase in Tregs followed by decline
- sustained high and expanded TCR clonality
- rising exosomal PD-1 and CD28 expression
- high baseline PD-L1 levels (>1.5 ng/ml) in anti-PD-1 but not anti-CTLA4

*J.R. Thompson and S. P. Menon (2017) Cancer J. 24, 78

Increased Frequency of Circulating of $CD14^{+}CD16^{-}HLA\text{-}Dr^{hi}$ Monocytes and Association with Positive Response to Anti-PD-1 Immunotherapy in Stage IV Melanoma



From: C. Kreig et al. (2018) Nature. Med 24, 144

Systemic Predictive Markers for ICB Therapy

- peripheral blood neutrophil to lymphocyte ratio greater than five associated with decreased PFS and OS across multiple cancer types
- high circulating T cell BIM levels (BCL-2 interacting mediator of cell death) association with poor prognosis and low likelihood of ICB response

Immune Suppression by Cancer-Derived Exosomes

- exosomal PD-LI suppression of $CD8^+$ T cells
- decreased production of immunostimulatory molecules
  - IL-2, IL-17 and IFN-γ
- increased levels of immune inhibitory proteins
  - TGF-β, IL-10, COX-2
- miR212 induction of reduced MCH II expression
- miR222, miR494 and M1 to M2 shift in tumor associated macrophages
- immunosuppression of B cells by exosome membrane-associated CD39 and CD73 via production of extracellular adenosine
- impaired differentiation of DCs from bone marrow precursors
- enhanced survival of MDSC via activation of STAT3
- inhibition of NK cells by exosome surface MICA/MICB liquids, TGF-LAG and induction of inhibitory TGF-β

Peripheral T Cell Dynamics in Neoadjuvant anti-PD-1 Blockade in NSCLC *

- opportunity for neoadjuvant Rx to assess major pathological responses (MPRs)
- dynamic remodeling of peripheral TIL clonotypes post-Rx
- TIL clonotypes detected in peripheral blood at significantly higher frequency than intratumoral clonotypes

*J. Zhang et al. (2018) SITC Abstract 047

Commensal Microbiota and ICB Responses

- diversity and composition of gut but not oral microbiota influence response in mice and humans
  - NSCLC, RCC, melanoma and urothelial cancer
- decreased response in patients treated with antibiotics but not PPIs during ICB therapy
- adoptive transfer of response-associated bacteria to germ-free or antibiotic-treated mice conferred ICB sensitivity
  - different microbial species identified in different publications
  - different sequencing and metagenomic analysis methods
- major geographic variation in predominant gut microbiota phyla

Hyperprogressive Disease (HD) in Anti-PD-1/PDL-1 Immunotherapy

- reported variable incidence across different solid tumors (6% to 29%)
- discrimination of HD from naturally aggressive disease and pseudoprogression
- requires integration of dynamic estimates of tumor growth rates (TGR)
  - TGR = estimate of increase in tumor volume over time between two CT scans assuming exponential growth
- TGR algorithms publically available on line but not integrated into majority of imaging software packages in routine use

*S. Champiat et al. (2018) Nat. Rev. Clin. Oncol. 15, 749

Combination Immunotherapies

Combination Immunotherapy in Cancer

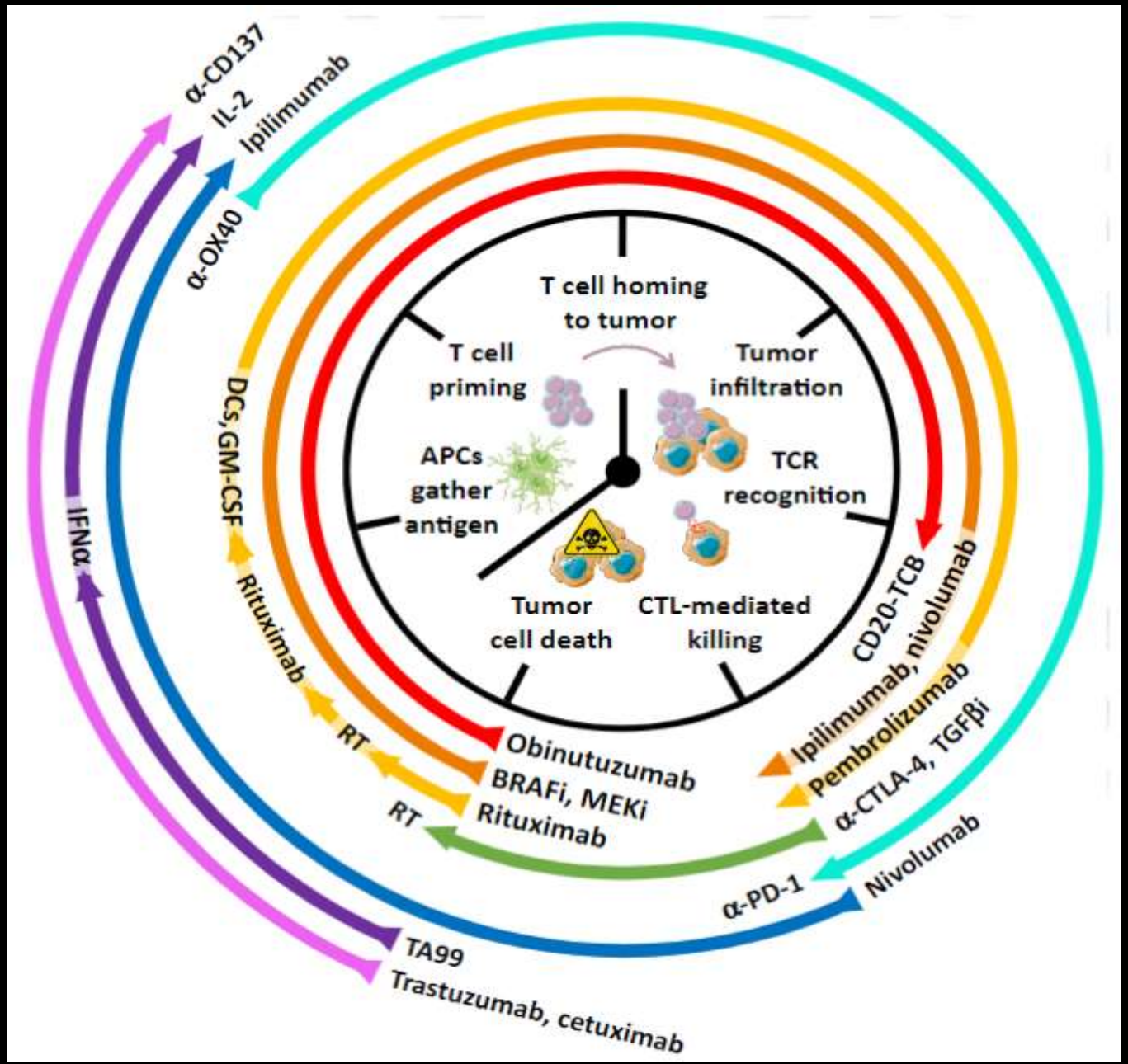
- new neoadjuvant protocols
- amplification of neoantigen exposure by cytotoxic agents, oncolytic viruses
- stimulation of innate immune system and type 1 IFN signaling to enhance priming/activation of adaptive immune responses
- co-stimulation of $CD8^+$ and $CD4^+$ cells by agonist OX40, GITR or 4-1BB antibodies
- STING stimulation of dendritic cells to produce IFNβ
- use of drug delivery scaffolds for extended release of agonists

The Design of I/O Combination Clinical Trials

- combine agent with non-redundant MOAs and different targets
- need for evidence of efficacy as single agent as rationale for anticipated additive/synergistic efficacy?
  - cf. IDO1 inhibitor implosion
- dose, duration and sequence of administration
- approved dose for each agent or dose escalation titration?
- validation of preclinical models for new I/O agent discovery and evaluation of combination options (efficacy/safety)
  - allometry extrapolation for dose, duration, PK
  - shared human: murine immune determinants versus human-specific targets with need for humanized immune system mouse models

Chronobiology and Chronopharmacodynamics: Neglected Variables in Immunotherapy?

Framework for Temporally-Programed R_x Combinations in Cancer Immunotherapy



From: A.M. Rothschilds and K.D. Wittrup (2019) Trends in Immunol. 40, 1 https://doi.org/10.1016/j.it.2018.11.003

Chronobiology of Immune Response Timescales and Rational Design of Combination Therapies Using Animal Models

- $CD4^+$ T cells exposed to IL-1 prior to priming/co-stimulation impairs activation, proliferation and memory formation
- expression of high affinity IL-2R on $CD8^+$ T cells after activation is transient (versus Treg in which expression is constitutive)
  - implications for pulsatile versus continuous infusion
- brief IFN signaling induces activation of $CD8^+$ cells but persistent signaling confers ICB resistance
- dosing of IFNα two days after IL-2 and cytotoxic Rx enhances tumor eradication versus simultaneous co-administration
- concurrent anti-PD-1 blockade negates effect of agonist OX40 antibody

Chronobiology of Immune Cell Trafficking Patterns:* Potential Implications for Immuno-Pharmacodynamics?

- circadian oscillations in number of circulating immune cells and trafficking to lymph nodes (LNs) and tissues
- T and B cells express classic circadian core clock genes
- circulating lymphocyte numbers peak around Zeitgeber Time 5 (ZT) (5 hrs after light onset)
- $CD4^+$ and $CD8^+$ cells exhibit peak LN levels at ZT13
- expression of CCR7 on HEV in LNs exhibits parallel rhythmicity
- lymphocyte egress from LN to efferent lymph regulated by circadian expression of sphingosine-1-phosphate receptor 1 (S1P1R)
- engineered deletion of core clock gene Bmal1 in T cells ablates circadian rhythmicity

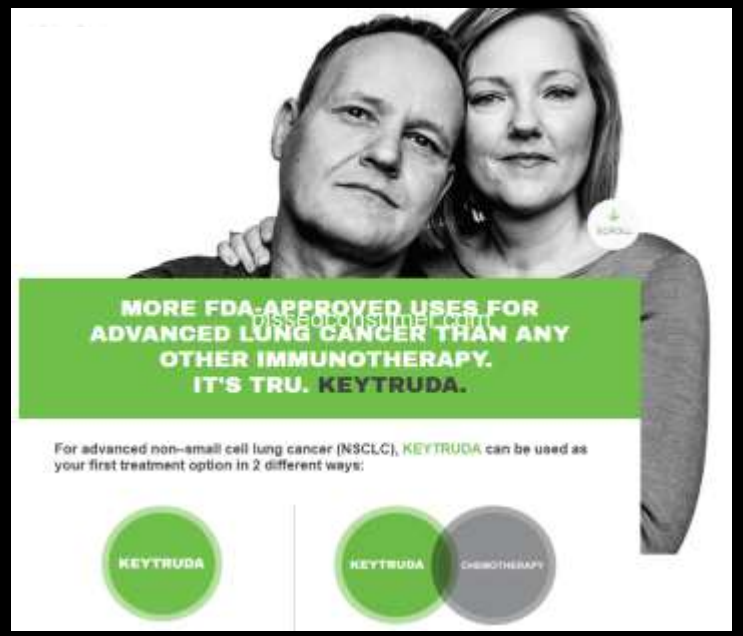
D. Druzd et al. (2017) Immunity 46, 120

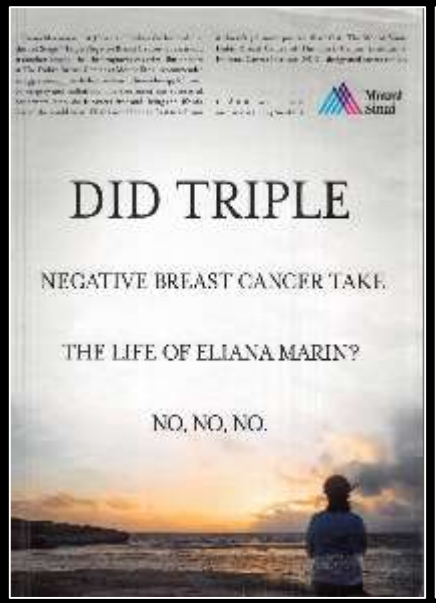
Is the Unrestricted Use of Immunotherapy With Current High Non-Responder/Failure Rates Economically Sustainable?

The Looming Expansion of the ‘Baby Boomers’ Cancer Burden

Expensive Industry DTC Advertising Campaigns

Hype Versus Hope: A Delicate Ethical Balance Come and Be Cured by Us: (Go Elsewhere at Your Peril)!

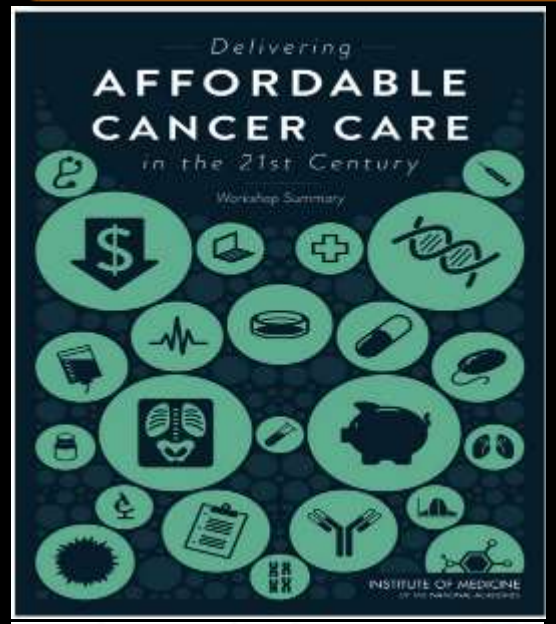


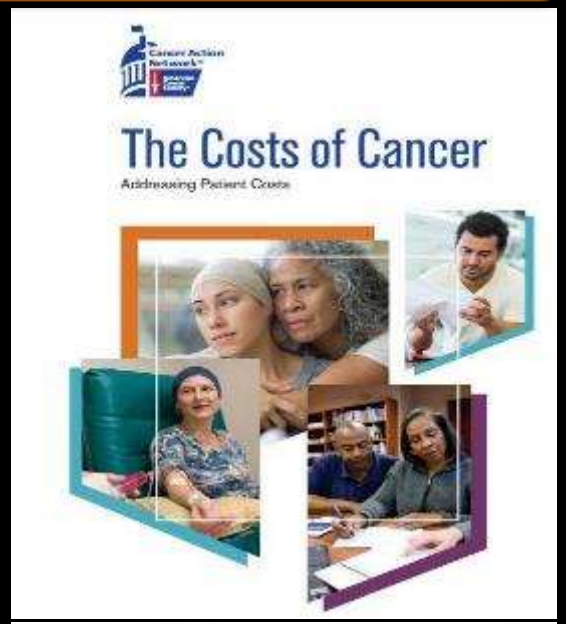


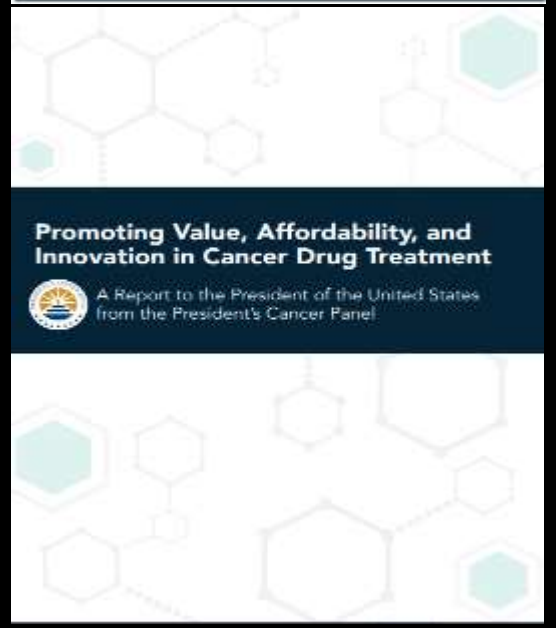
Immunotherapy: Hype and Hope

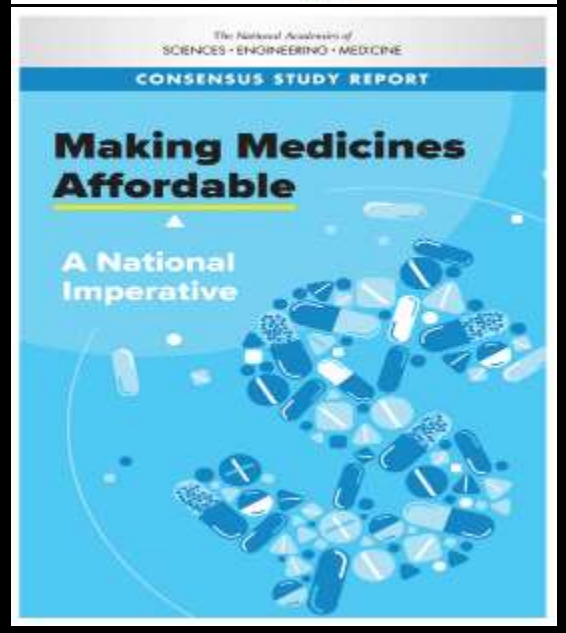
- deserved recognition of ICB as major therapeutic advance
- media hype, scale of corporate DTC and AMC advertising campaigns
  - biased emphasis on responder/super-responders distorts public awareness of NR>R and potential for serious toxicities
  - unrealistic patient expectations of successful outcome
- patient demands for immunotherapy despite no evidence of efficacy in their specific malignancy

Cancer Treatment Cost







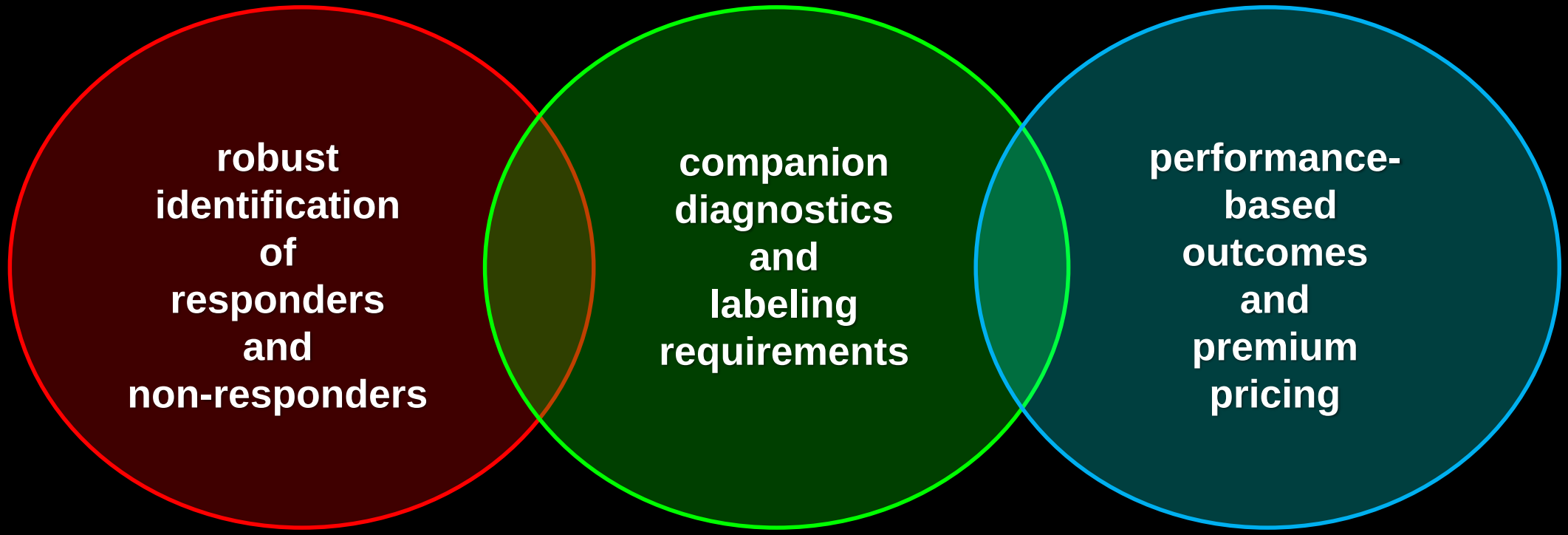


Value Framework

Is the Bar in the ASCO Value Frameworks Too High in Assessing Long-Term Benefits in I/O Therapy?

- JAMA Oncology (2018) 4,326
  - analysis of approved I/O agents (2011 to 8/17)
- 23 indications for 6 I/O agents for metastatic solid tumors
- only 3 gained durable survival bonus points under ASCO framework

Performance-Based Contracts and Pricing: The Inevitable Future Landscape for Immunotherapy?



integration of R:NR immunophenotypes into clinical trials and registration dossier

risk sharing

The Urgent Clinical and Economic Imperatives for Predictive Markers to Differentiate Responder and Non-Responder Patients in Different I/O Regimens

- single most important opportunity for the (bio)pharmaceutical industry?
- increased payer pressure for performance-based outcomes?
- premium pricing for proactive industry engagement or reactive response to payer imposition of outcomes-based reimbursement?

Biomarkers for Prediction and Prognosis in Cancer Immunotherapy

- single biomarkers versus composite biomarker score
- static versus dynamic immuno-profiling
- standardized immuno-profiling methods (eg. TMB cutoffs)
- large N cohorts for clinical validation and utility
- validation of cross-study cohort comparisons based on standardized profiling methods and similarity of (pre)treatment regimen/duration
- extended longitudinal monitoring for OS
- machine learning algorithms for multiparameter composite scores and deconvolution of independent and inter-dependent indicators
- regulatory standards for complex multiparameter Dx-software platforms for prediction and prognosis (monotherapy and combination therapy)

Slides Available @ http://casi.asu.edu/presentations