Predictive Biomarkers and Treatment Individualization

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Disclosures

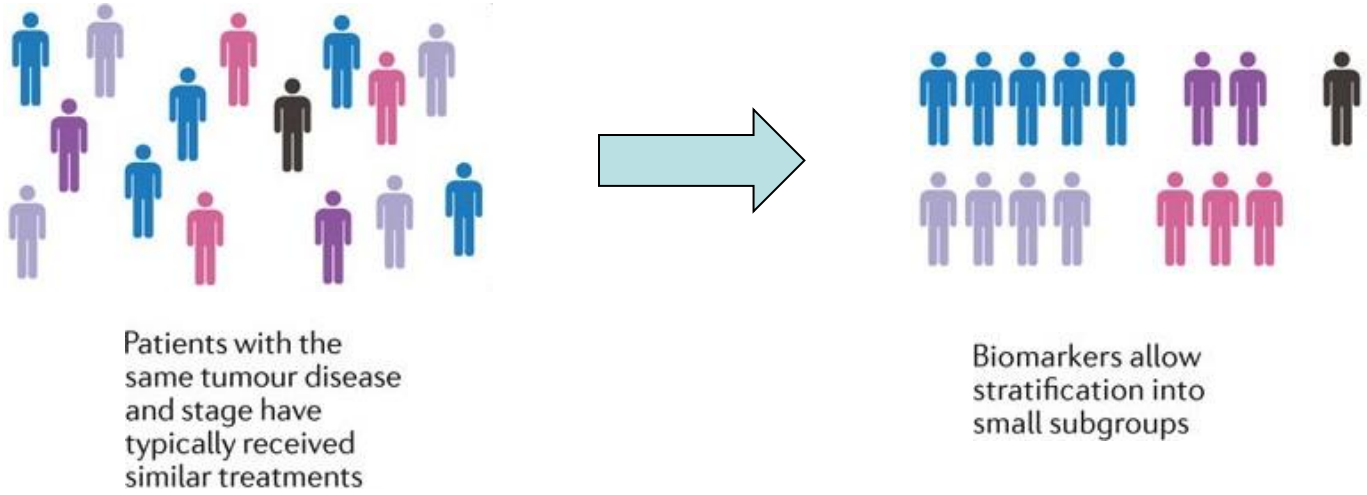
Patents/Licensing: Roche, Adela

Ownership: Adela

Learning Objectives

- Describe the concept of personalized radiation medicine based on biomarkers.
- Distinguish between prediction versus prognostic biomarkers.
- Understand examples of molecular and imaging biomarkers used in radiation oncology.

Role of Biomarkers in Precision Radiation Medicine



Baumann, Nature Rev Cancer 2016

What is a “Biomarker”

- **Biomarker:** Characteristic that is objectively measured as an indicator of a biologic processes or a responses to a therapeutic intervention
- **Assay:** Method for determining the presence or quantity of a component
- **Test:** Procedure that makes use of an assay for a particular purpose

A Renaissance of Biomarker Research

MEDIUM

Tissues
(Normal & Malignant)

Biofluids
(Blood, Urine, etc.)

Imaging
(Anatomic, Functional, etc.)

SOURCE

Tumour Cells
(Primary & metastasis)

Host (Normal) Cells
(Healthy tissues)

Tumour Microenvironment
(Vasculature, immune infiltrates, etc.)

ENABLERS

New Technologies
(DNA sequencing, etc.)

Clinical Trials
(Improved infrastructure)

Relevant Endpoints
(Efficacy, toxicity, QOL, cost, etc.)

Examples of Biomarkers

Setting	Biomarker
Risk of developing cancer	BRCA carrier Clonal hematopoiesis
Screening & diagnosis	Mammogram
Prognosis	Oncotype Dx for ER+ breast ca HPV in head & neck ca
Predictive of treatment benefit/harm	ER/PR HER2
Monitor disease burden and treatment effect (dynamic biomarker)	PSA ctDNA (e.g., EBV DNA)
Surrogate endpoint for efficacy	MRI, PET PSA

Therapeutic Biomarkers

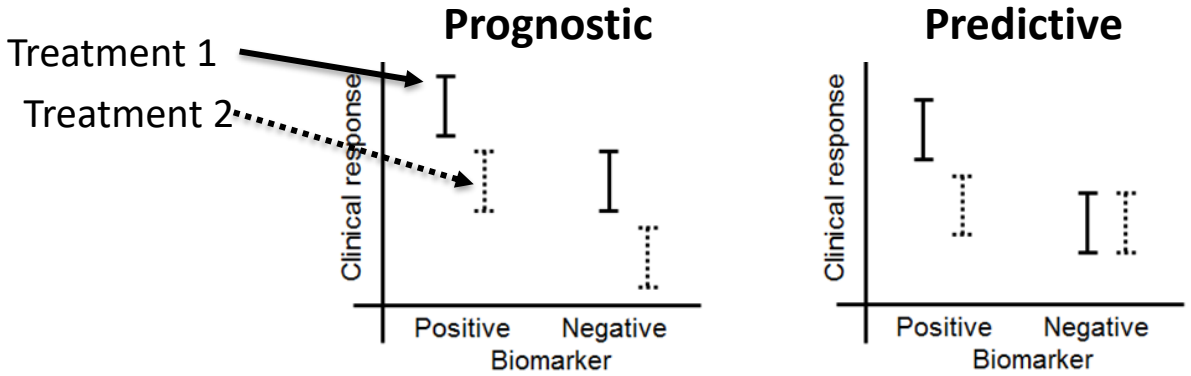
Purpose of Therapeutic Biomarkers

- Many cancer treatments benefit only a small subset of patients
- Treatments should be targeted to the patients that can derive clinical benefits in order to:
  - Maximize therapeutic index
  - Reduce health care costs associated with unnecessary treatments and toxicities

Prognostic vs Predictive Biomarkers

Prognostic biomarker: provides information on *the likely course of the cancer disease in an untreated/similarly treated individual(s)*.

Predictive biomarker: can be used to *identify subpopulations of patients who are most likely to respond to a given therapy.*



Therapeutic Biomarkers: *Validation*

- Analytical validation
  - Compare to gold standard to determine repeatability, accuracy, robustness, etc.
- Clinical validation
  - What are the associations of the biomarker with clinical endpoints (e.g., survival, toxicity, etc.)
- Clinical utility
  - Does use of the biomarker result in patient or societal benefits
  - Depends on clinical context/use of the biomarker

Biomarkers in Clinical Trials

- Retrospective Designs
  - Hypothesis generation studies
    - Retrospective analyses based on convenience samples
  - Prospective/retrospective designs
    - Can be used for clinical validation

- Prospective Designs to demonstrate utility
  - Target selection (enrichment) designs
  - Marker by treatment interaction designs (biomarker stratified design)
  - Biomarker-strategy designs

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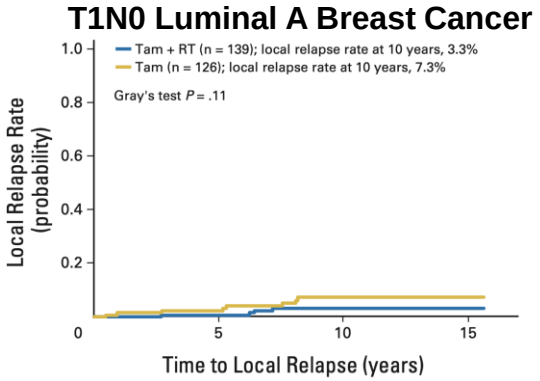
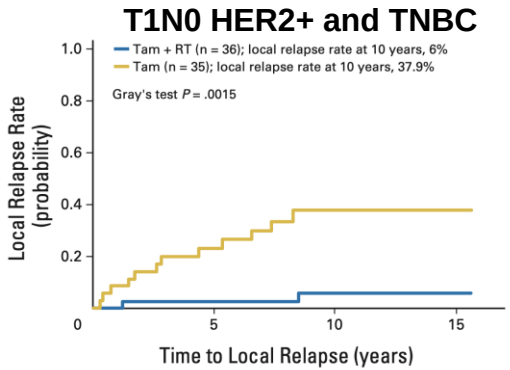
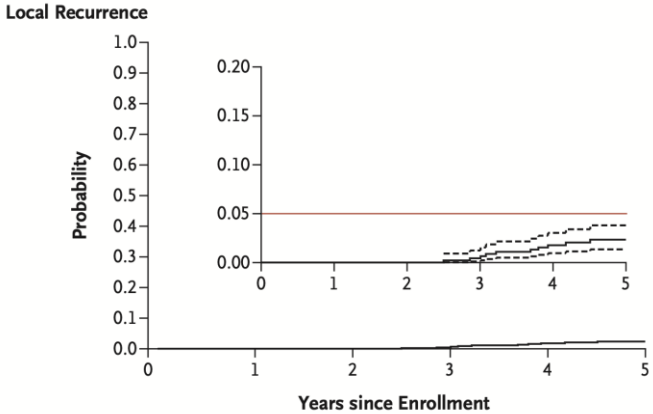
Biofluids (Blood, Urine, etc.)	**Host (Normal) Cells** (Healthy tissues)	**Clinical Trials** (Improved infrastructure)
Imaging (Anatomic, Functional, etc.)	**Tumour Microenvironment** (Vasculature, immune infiltrates, etc.)	**Relevant Endpoints** (Efficacy, toxicity, QOL, cost, etc.)

Tissue-Based Biomarkers





- **Is this a prognostic or predictive biomarker?**
- **How could clinical utility be demonstrated?**
- **Target selection clinical trial:**



Liu FF, Fyles T, et al. JCO 2015;33(18):2035-40
Whelan et al. NEJM 2023;389:612-9

Prostate Cancer Tissue-Based Biomarkers

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
Prostate Cancer

NCCN Guidelines Index
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Discussion

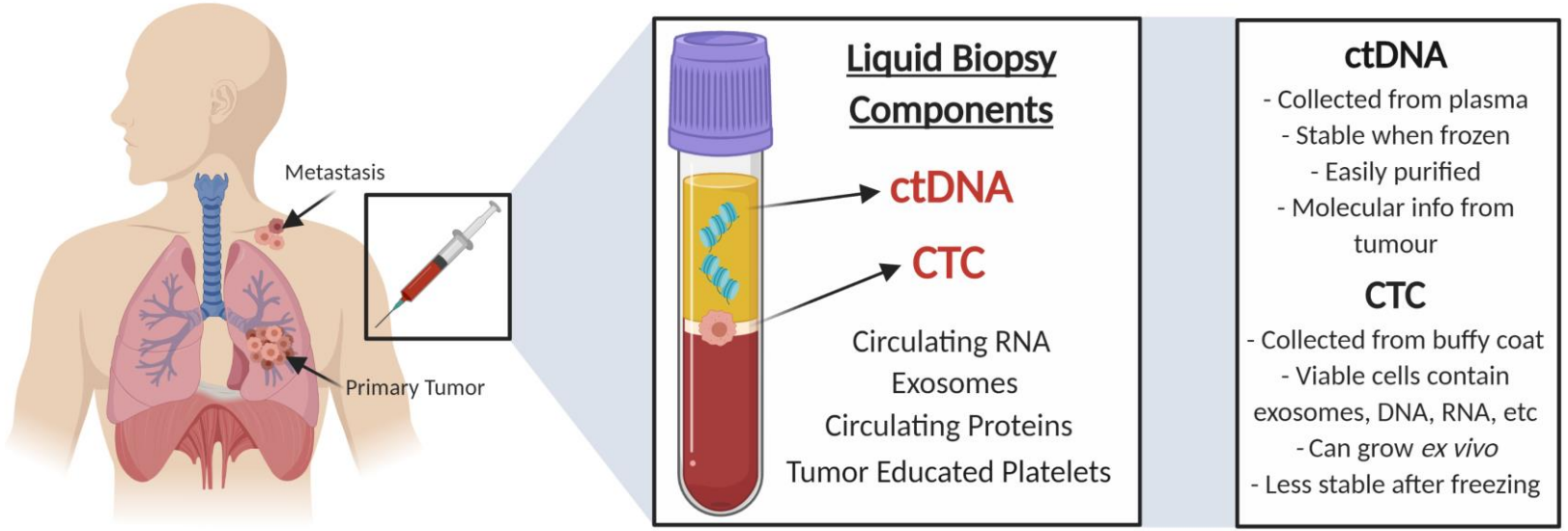
PRINCIPLES OF RISK STRATIFICATION

Table 2. Risk Stratification: Selected Advanced Tools for Localized Prostate Cancer

Category	Tool	Predictive	Prognostic	Prognostic Endpoint Trained For[f]	Simon Level of Evidence[1,d]	Treatment Implications
Gene Expression						
	22-gene genomic classifier (GC) (Decipher)	No	Yes	Metastasis	IB	See Table 3
	31-gene cell cycle progression (CCP) assay (Prolaris)	No	Yes	See footnote[g]	IIIC[i]	
	17-gene Genomic Prostate Score (GPS) assay	No	Yes	Adverse pathology	IIIC	
AI Pathology						
	Multimodal artificial intelligence (ArteraAI Prostate)	Yes	Yes	BCR, DM, PCSM[h]	IB Predictive IB Prognostic	See Table 3
Germline						
	HRD	No	Unclear	—	VD	
Risk Stratification: Selected Advanced Tools Post-RP						
Gene Expression						
	22-gene GC	No	Yes	Metastasis	IB	See Table 3
	31-gene CCP assay	No	Yes	See footnote[g]	IVD	
	17-gene GPS assay	No	Yes	Adverse pathology	IVD	

HRD = Homologous recombination deficiency, DM= distant metastases, PCSM = Prostate cancer-specific mortality

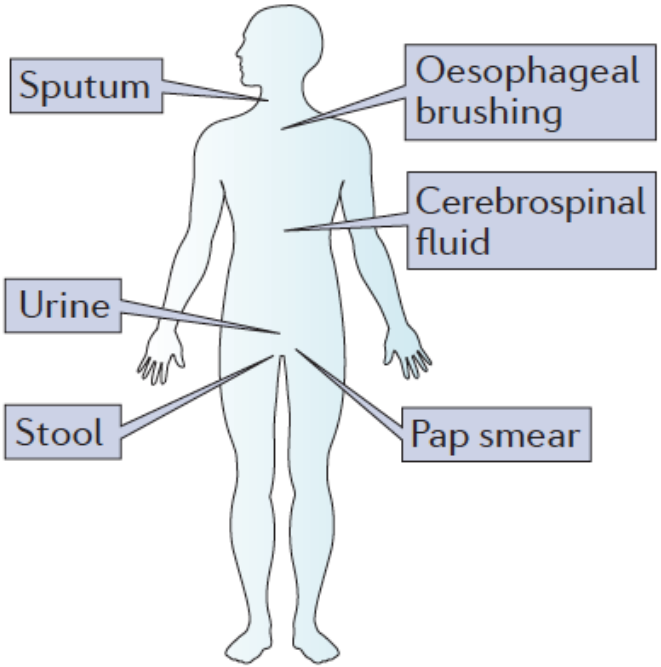
Examples of Blood-Based Biomarkers



ctDNA: circulating tumor DNA
CTC: circulating tumor cell

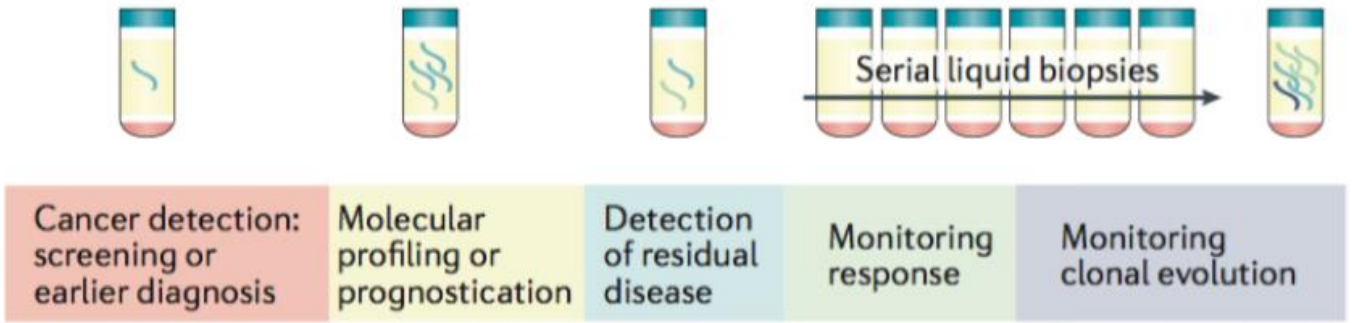
De Michino, Lok, Bratman et al. IJROBP 2020; 107(5),873-886

Examples of Other Biofluid Sources



Wan…Rosenfeld et al. Nat Rev Cancer 2017

Could ctDNA have utility across the cancer care continuum?



Wan…Rosenfeld et al. Nat Rev Cancer 2017

ESMO recommendations on the use of ctDNA

- **For advanced cancers, validated and adequately sensitive *ctDNA assays have utility in identifying actionable mutations to direct targeted therapy*, and may be used in routine clinical practice, provided the limitations of the assays are taken into account**
- **For early-stage cancers, detection of molecular residual disease (MRD) has high evidence of clinical validity in anticipating future relapse, but MRD detection cannot be recommended in routine clinical practice due to lack of clinical utility studies**
- **Additional potential applications of ctDNA assays are not recommended for routine practice**

Imaging Biomarkers

- Anatomical imaging
  - Computed tomography (CT), magnetic resonance imaging (MRI), ultrasound
- Functional & molecular imaging
  - MRI, contrast enhanced imaging, radiotracer positron emission tomography (PET), etc.
- Dynamic imaging
  - Changes during or between scans
  - Behavior of injected contrast agents
- Quantitative image analysis & radiomics

Fluorodeoxyglucose (FDG)-PET

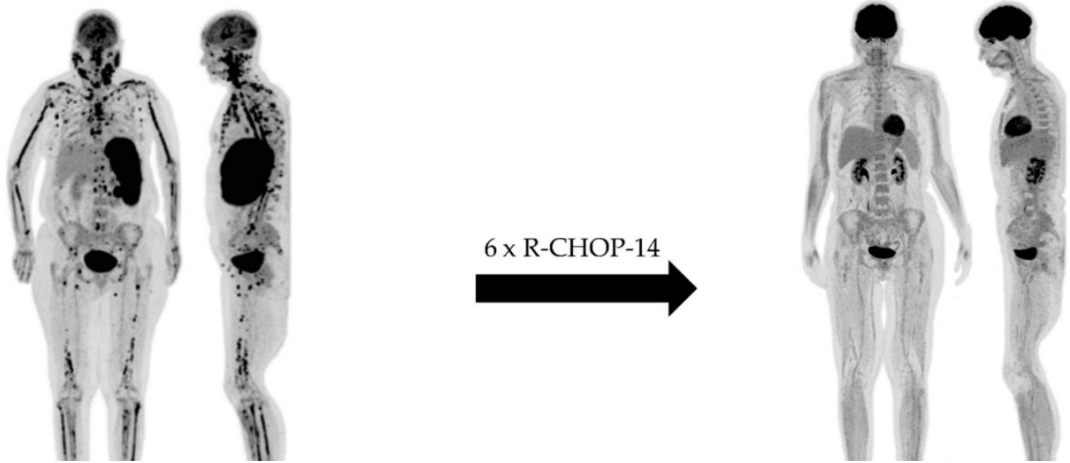
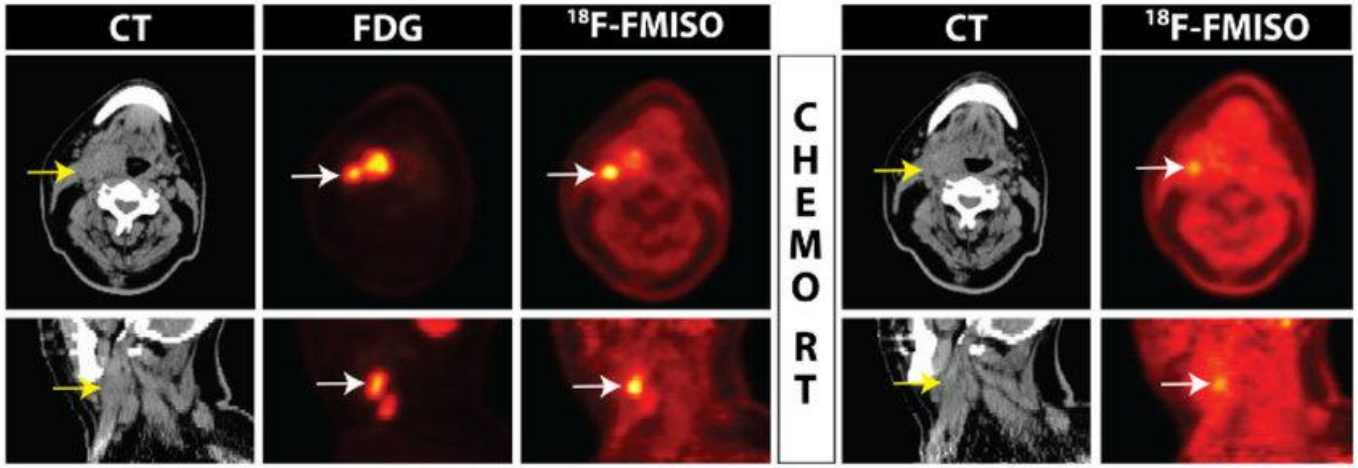


Table 3. Evidence-based recommendations on the use of FDG-PET before, during, and after treatment.

Indication	Hodgkin Lymphoma	DLBCL
Staging	+ + +	+ + +
Early response assessment	+ +	+ +
End-of-treatment	+ +	+ +
Follow-up	+/-	+/-

* + + +, standard modality; + +, standard—depending on therapy protocol; +/-, optional—recommended in selected cases, e.g., suspected relapse.

Hypoxia PET Tracers

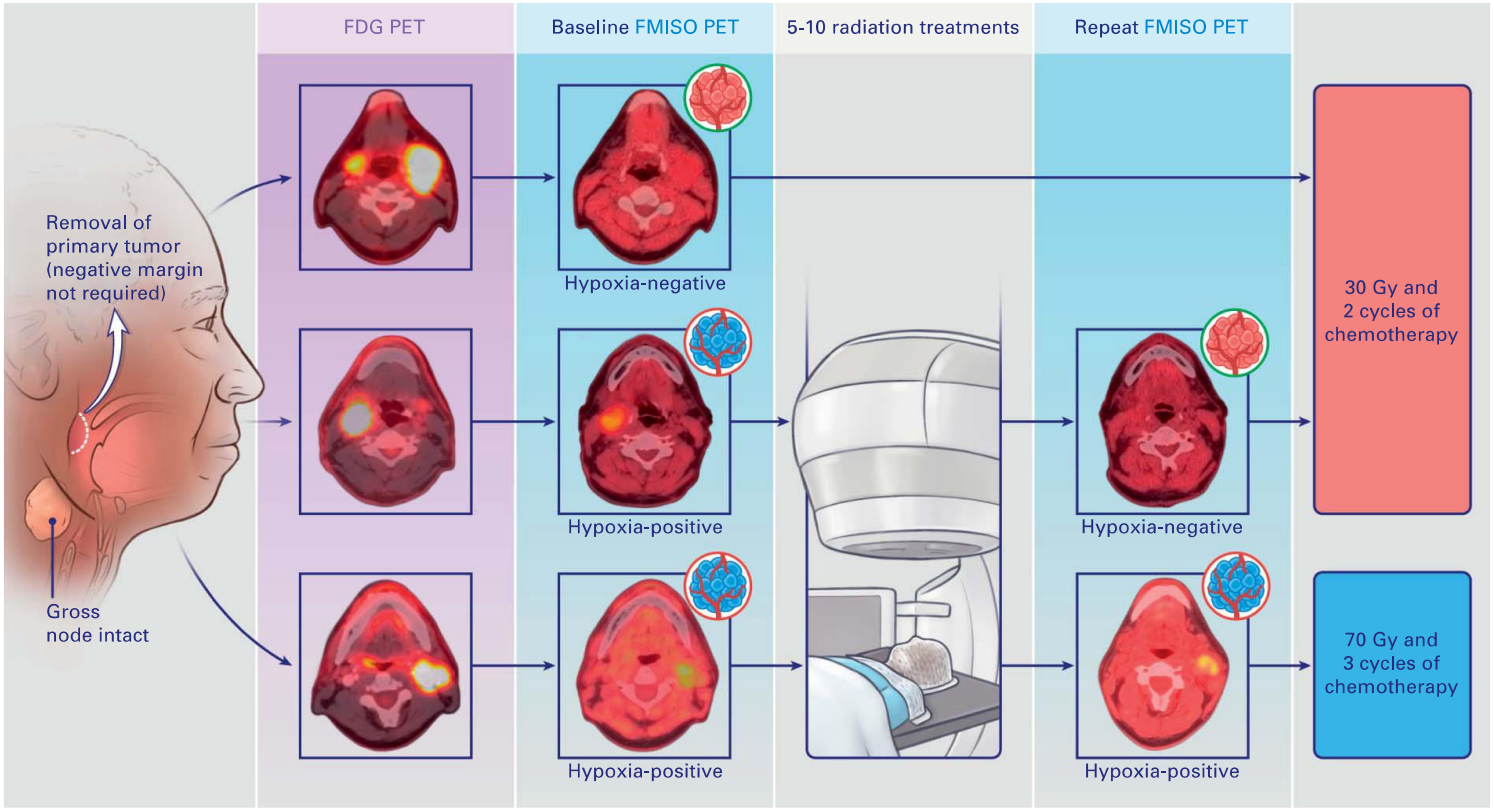


FDG: fluorodeoxyglucose
FMISO: fluoromisonidazole

Is tumor hypoxia a biomarker, assay, or test?

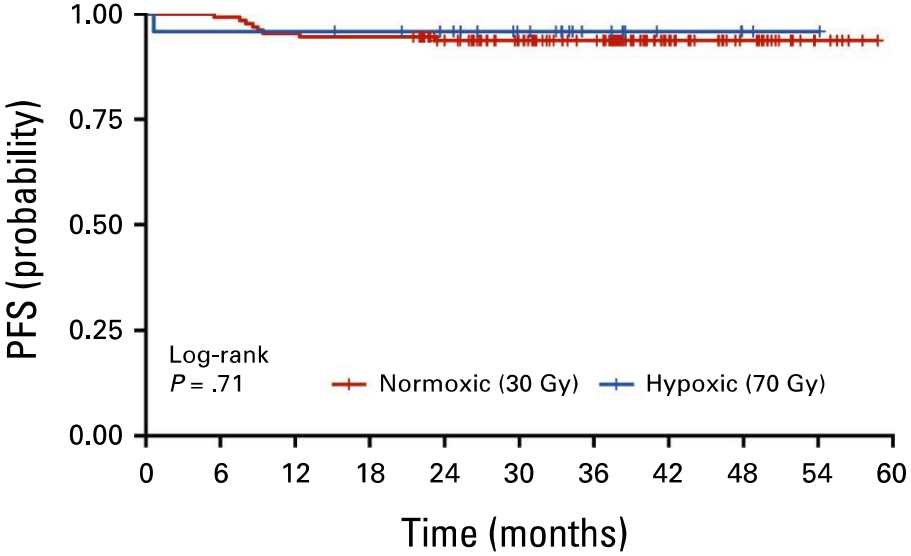
Lee N et al., Int J Radiat Oncol Biol Phys. 2016 Sep 1; 96(1): 9–17.

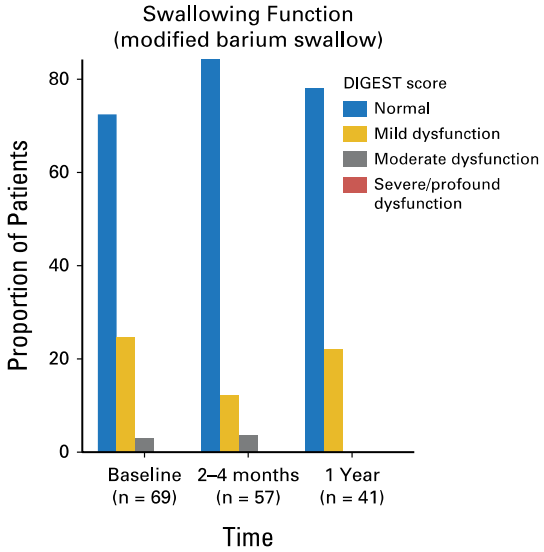
Hypoxia PET Tracers



Lee N, Riaz N et al., J Clin Oncol. 2024

Hypoxia PET Tracers

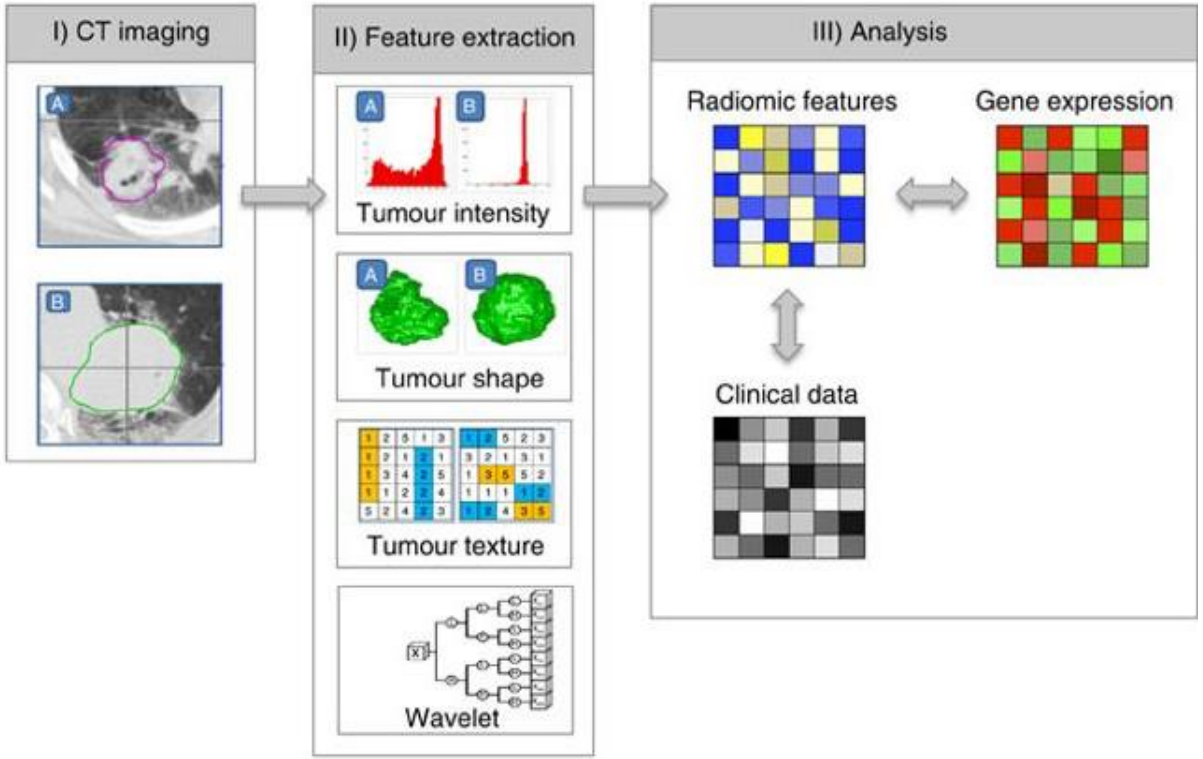




What type of therapeutic biomarker is hypoxia PET in this context?

Lee N, Riaz N et al., J Clin Oncol. 2024

Radiomics: Quantitative Image Analysis



Aerts et al., Nature Comm 2014

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Intrinsic Radiosensitivity as Predictive Biomarker for Radiotherapy Response

Disease Site	No. of Patients	SF2 Cutpoint	Outcome	Positive Study	Reference
Head and Neck	99	0.4	Local control <0.4 vs >0.4 91% vs 74% *P*=.036	Yes	Björk-Eriksson et al[8]
Cervix	128	0.42	Survival <0.42 vs >0.42 81% vs 51% *P*=.0002	Yes	West et al[6]
Head and Neck	38	0.5	Local control <0.5 vs >0.5 26% vs 45% *P*=NS	No	Stausbøl-Grøn et al[9]
Glioblastoma multiforme	50	Not determined	No correlation between SF2 and survival	No	Taghian et al[10]
Head and Neck	92	Not determined	No correlation between SF2 and survival	No	Eschwege et al[11]

Torres-Roca, Can Control, 2008

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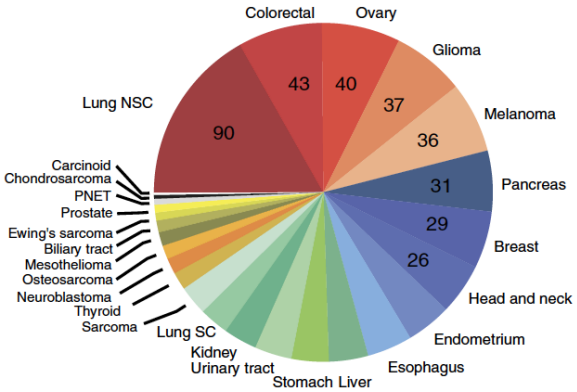
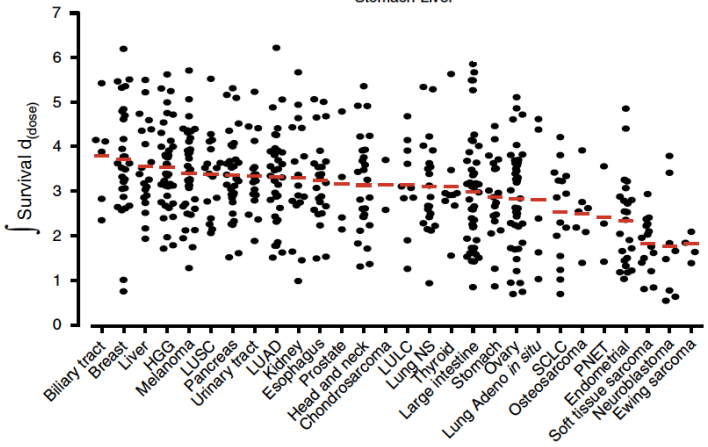
Torres-Roca, Can Control, 2008

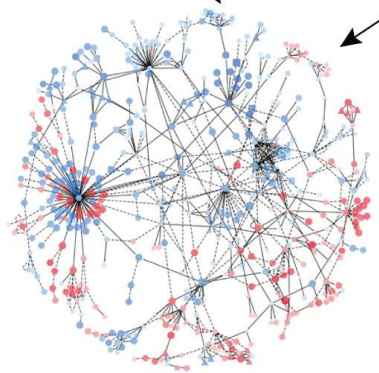
Why is SF2 not used in clinic?

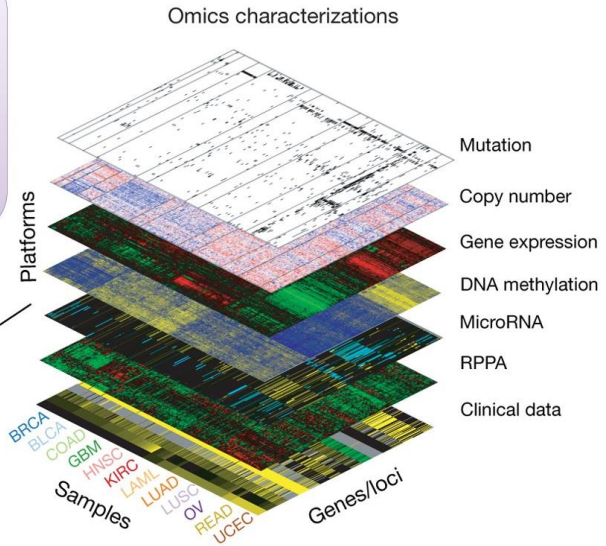
Searching for Molecular Surrogates for Radioresistance or Radiosensitivity





Thematic pathways



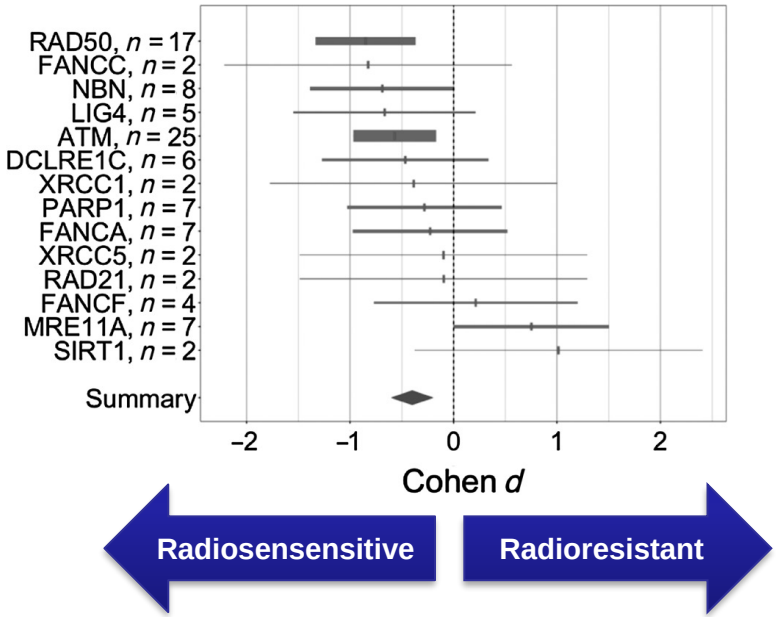


TCGA, Nature Genetics, 2013

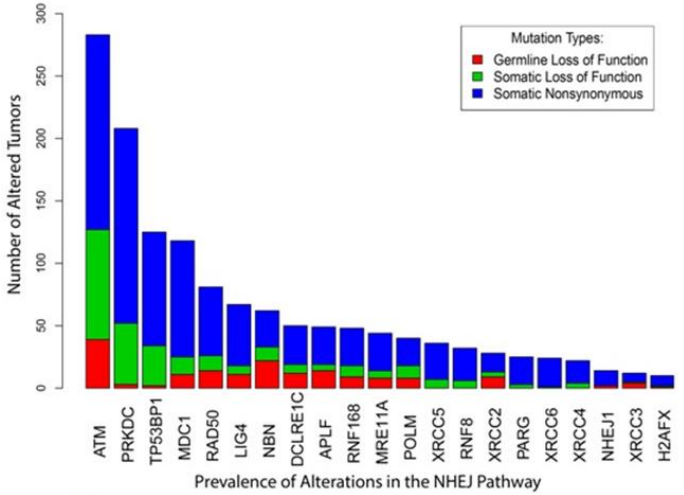
Abazeed, *et al*. (2013) *Cancer Res*
Yard, *et al.* (2016) *Nat Commun*

Importance of DNA Damage Repair

Association With Radiation Response in Cell Lines



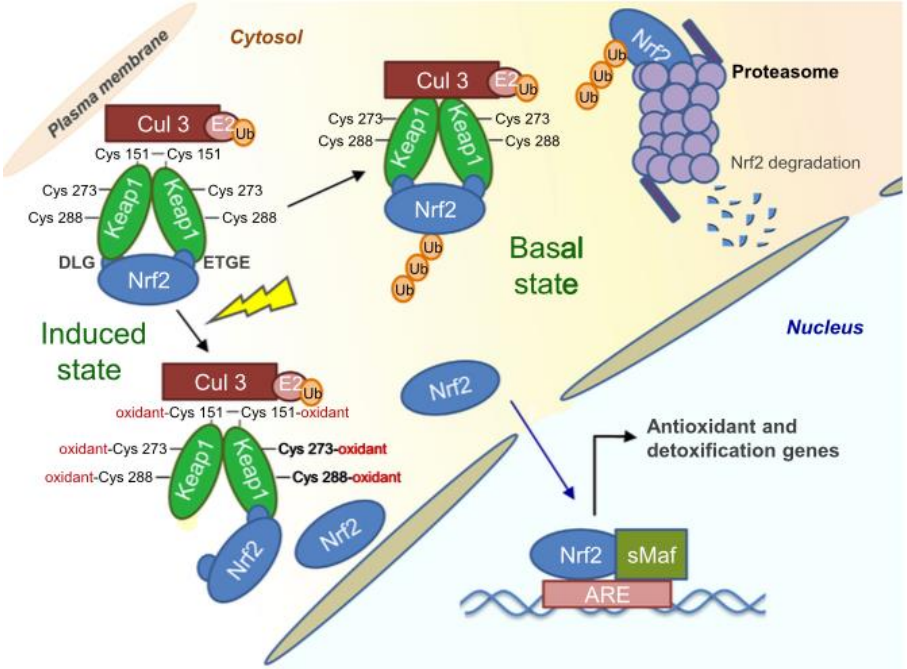
Mutation Prevalence in Cancer Patients (TCGA)



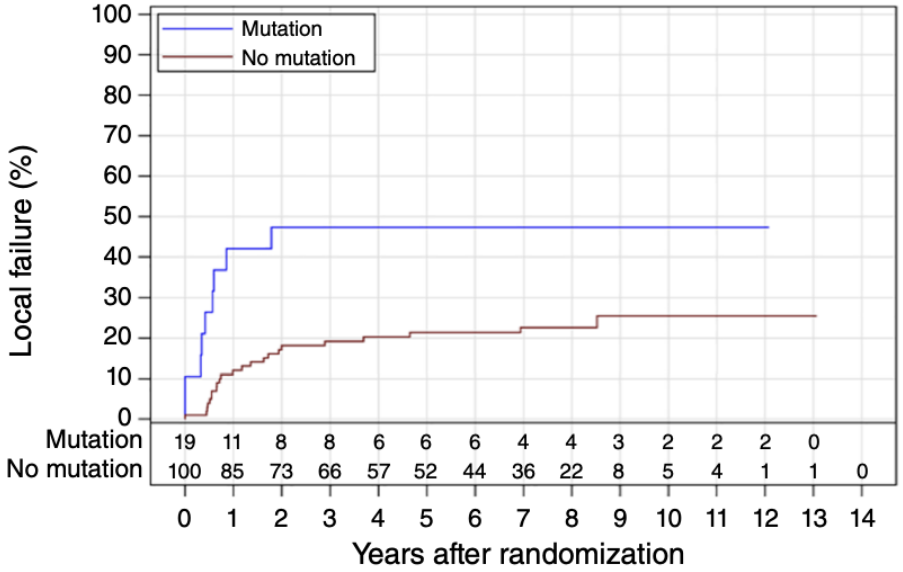
Manem…Bratman, *et al*. (2019) *Cancer Res*
Ma…Riaz, *et al.* (2017) *Oncotarget*

Importance of ROS scavenging

Nrf2/Keap1/Cul3 mutations increase ROS scavenging

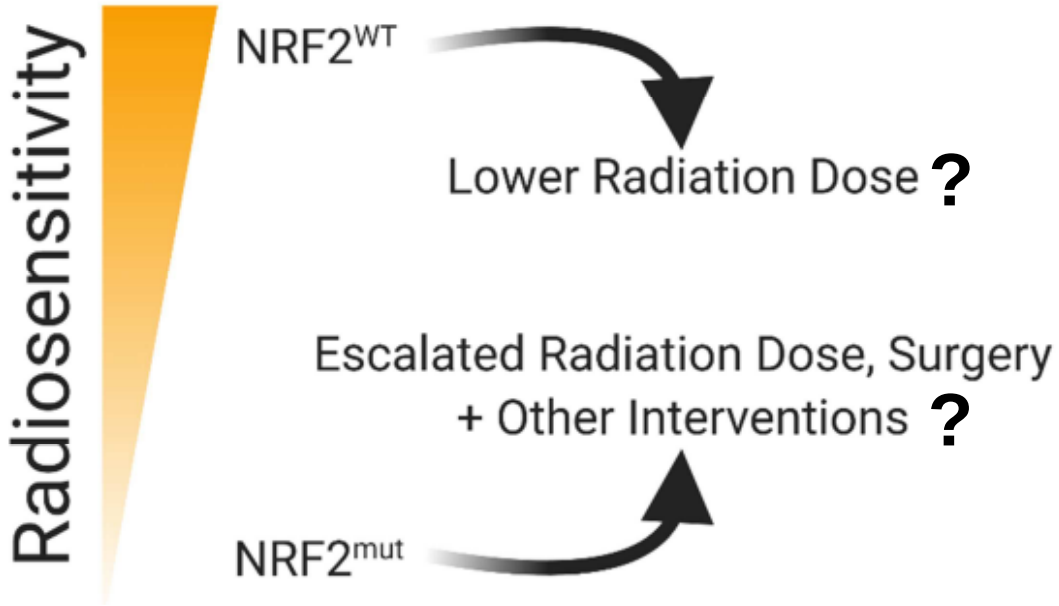


Nrf2/Keap1/Cul3 mutations in T2N0 larynx cancer

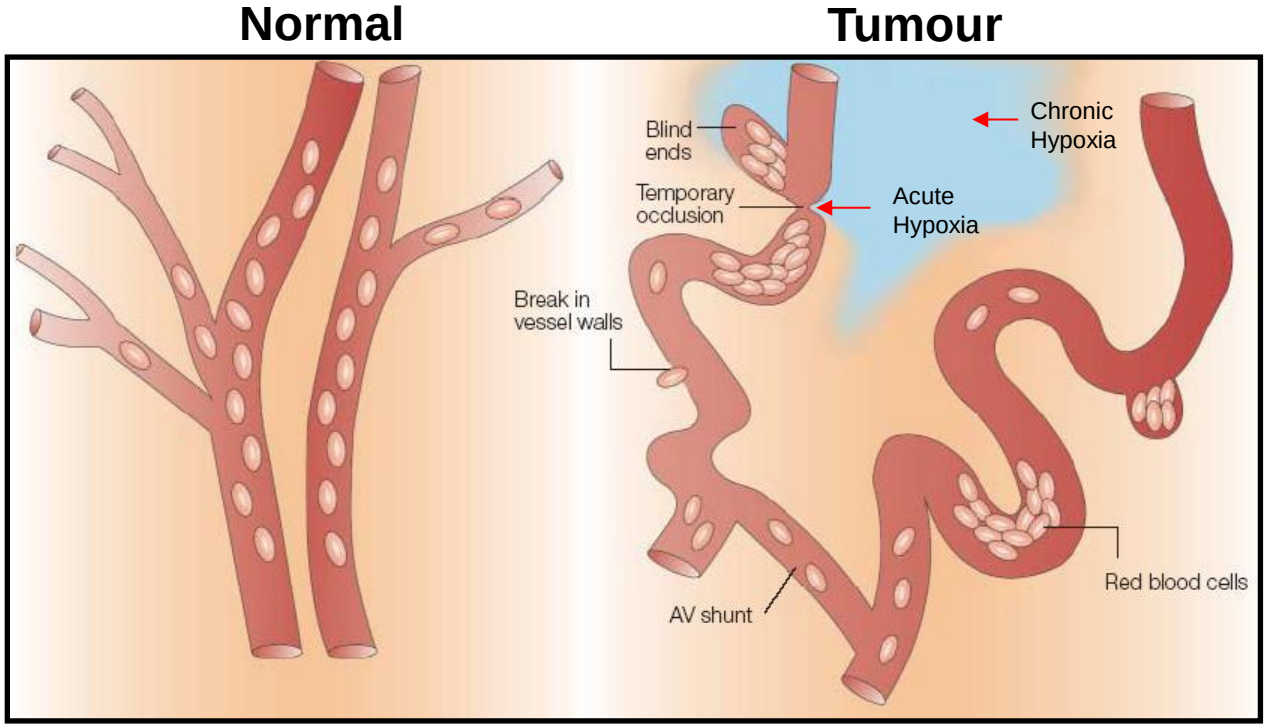


Espinosa-Diez, et al. (2015) Redox Biol
Guan, et al. (2024) Clin Cancer Res

Potential clinical actionability of NRF2 pathway mutations



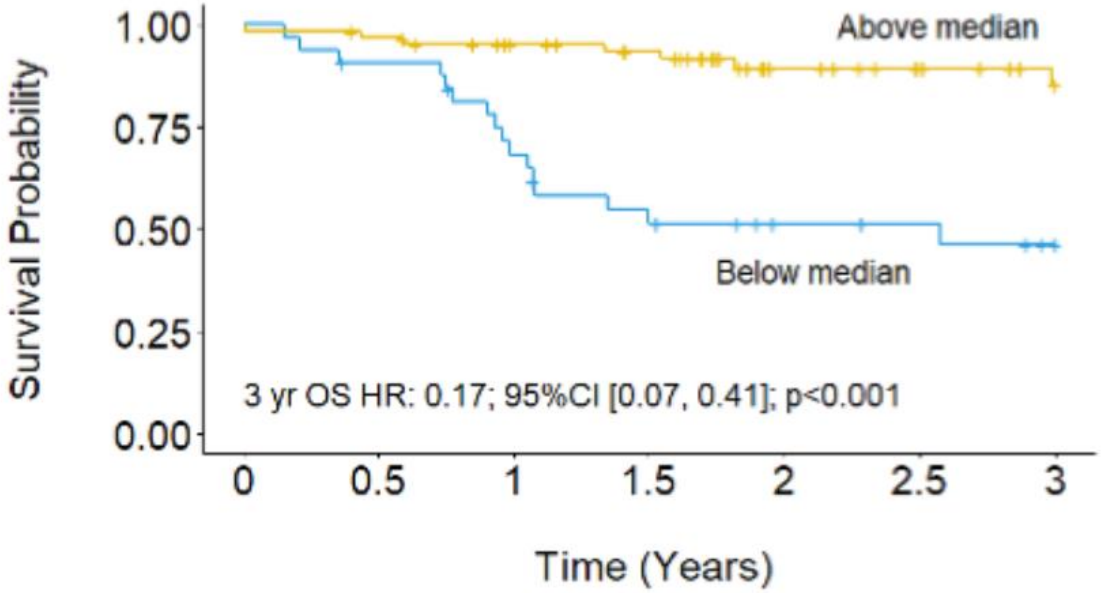
Microenvironment: Tumour Hypoxia



Adapted from Brown and Wilson; Nature, 2004

Microenvironment: Immune Cells

Infiltrating CD19+ B cells in HPV+ HNSCC



Kim, Sharabi, et al, CCR 2020

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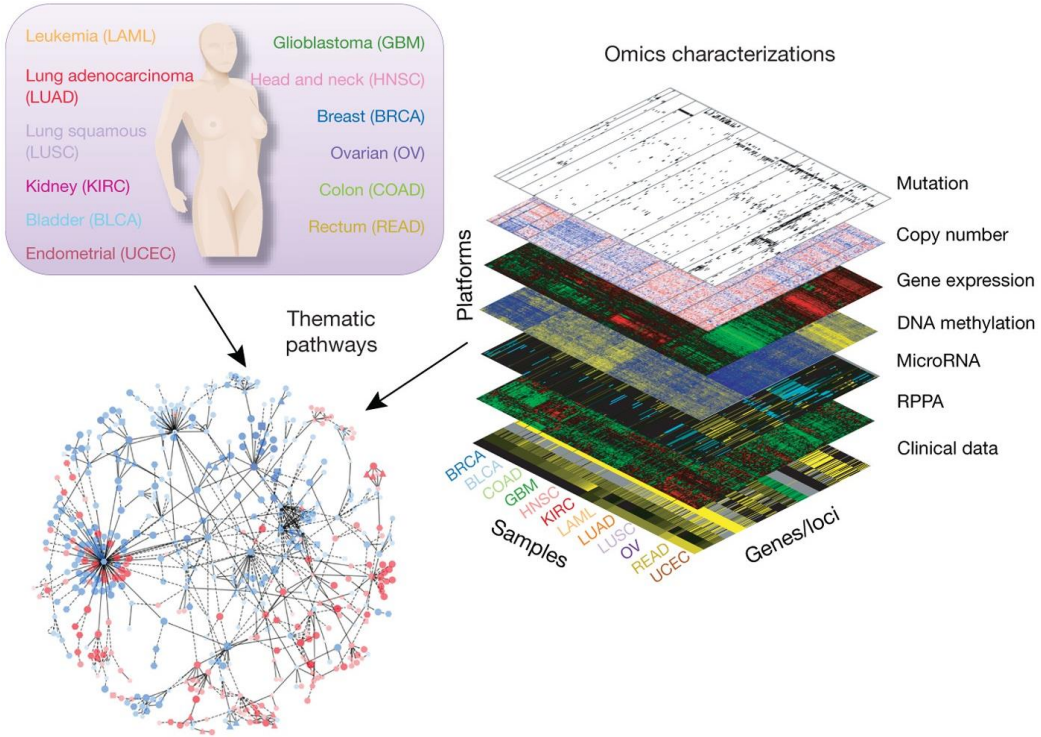
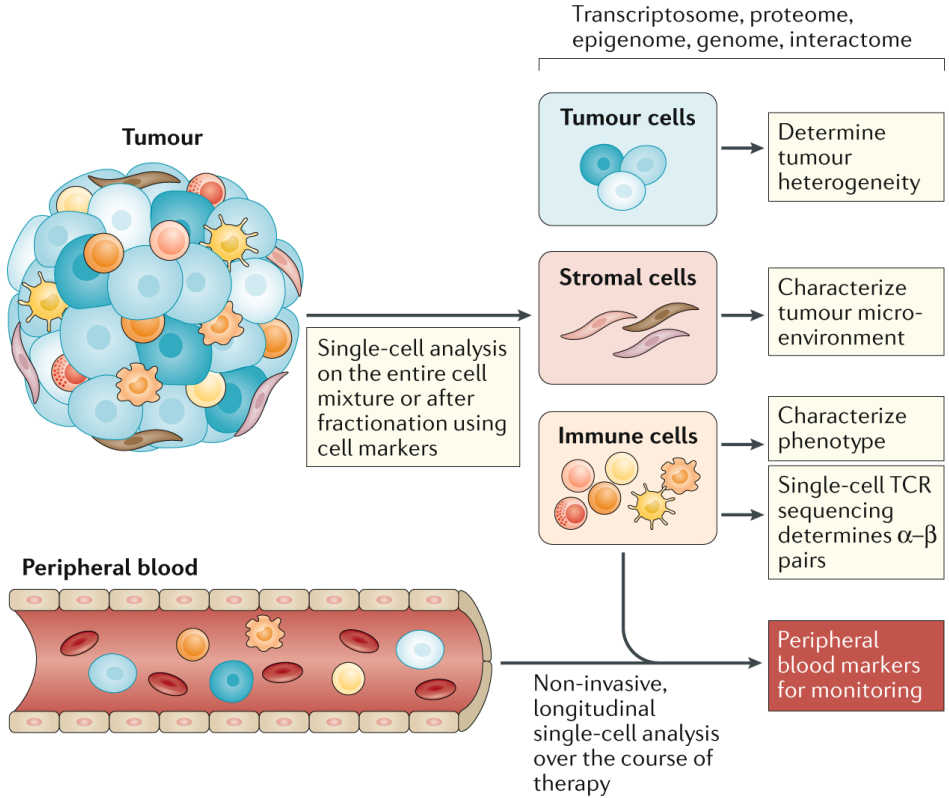
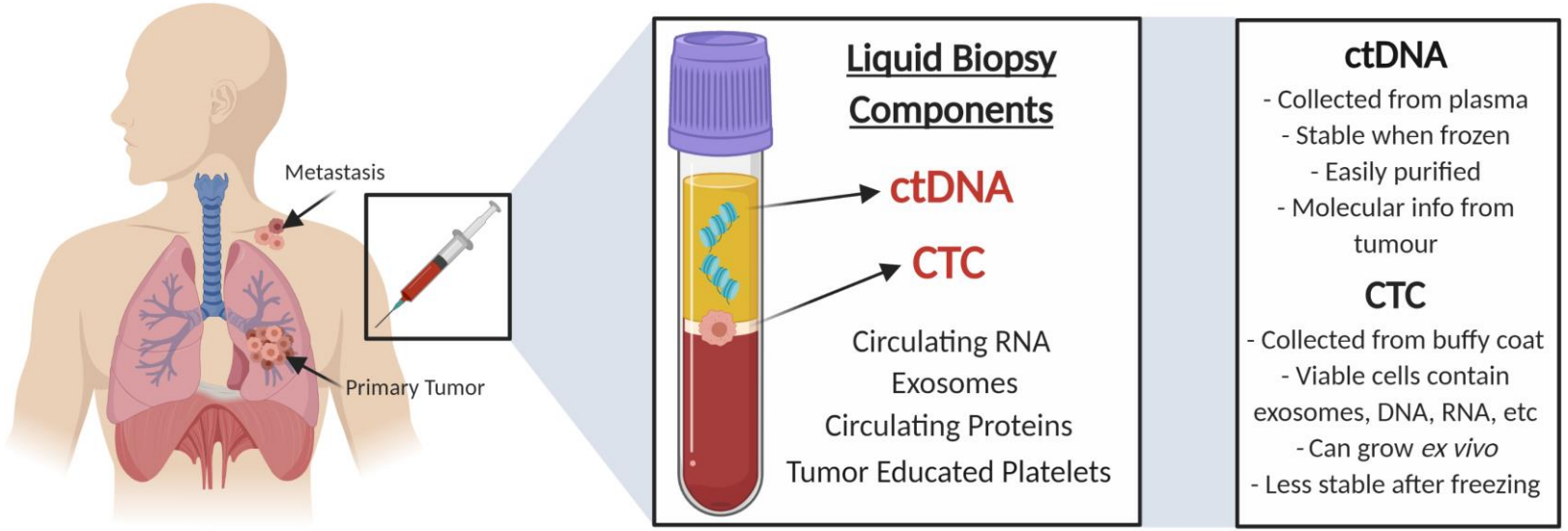
The Promise of -Omics



Deep Profiling of Individual Cells



Blood-Based Biomarkers



ctDNA: circulating tumor DNA
CTC: circulating tumor cell

De Michino, Lok, Bratman et al. IJROBP 2020; 107(5),873-886

PET Tracers for Molecular Functional Imaging

Table 1 Federal Drug Administration–approved molecular agents used in clinical oncology

Abbreviation	Tracer full name	Cellular target	Molecular basis	Clinical application(s)
^{18}F-FDG	Fluorine-18 fluorodeoxyglucose	Glucose metabolism	Increased rates of glycolysis overexpression of GLUT-1 and 3 receptors and increased levels of mitochondrial hexokinase in malignant cells	Tumor detection and staging Target volume delineation of multiple malignancies Monitoring of treatment response
^{18}F-NaF	Sodium fluorine-18 fluoride	Bone metabolism	Increased bone turnover in lytic and blastic bone lesions	Staging, follow-up of prostate cancer Bone metastases
^{18}F-FACBC or ^{18}F-fluciclovine	Fluorine-18 fluciclovine	Amino acid transport	Increased rates of amino acid transport	Biochemically recurrent prostate cancer
^{11}C-CHO	Carbon-11 choline	Lipid metabolism	Neoplastic cells exhibit increased levels of phosphorylcholine	Staging and follow-up of prostate cancers
^{68}Ga-DOTA -TOC -TATE	Gallium-68 DOTA-peptide	Somatostatin receptor	Somatostatin receptors are overexpressed in many tumors	Staging, follow-up, assessment for possible radioisotope therapy for neuroendocrine tumors and meningiomas
^{64}Cu-DOTATE	Copper-64 DOTATATE	Somatostatin receptor	Somatostatin receptors are overexpressed in many tumors	Staging, follow-up, assessment for possible radioisotope therapy for neuroendocrine tumors
^{18}F-FES	Fluorine-18 fluoroestradiol	Estrogen receptor	Estrogen receptors are often expressed in breast cancer	Detection of estrogen receptor–positive lesions as an adjunct to biopsy in patients with recurrent or metastatic breast cancer
^{68}Ga-PSMA-11	Gallium-68 ligand for the prostate-specific membrane antigen	Type II membrane protein	Prostate-specific membrane antigen inhibitor	Prostate cancers staging, follow-up, and ^{177}Lu planning
^{18}F-DCFPyL	Fluorine-18 ligand for the prostate-specific membrane antigen	Type II membrane protein	Enzymatic activity	Prostate cancer staging, follow-up, and biochemical recurrence evaluation

Summary

- Individualization of treatment can be done through risk stratification (prognostication) or through use of predictive biomarkers
- Sources of therapeutic biomarkers can be from tumour tissue, germline, bodily fluids, and imaging
- Prospective studies are needed to validate and prove utility of therapeutic biomarkers for use of radiotherapy
- Many novel biomarkers are being evaluated to maximize the therapeutic index

Questions?

Thank you!

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