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Biomarkers in oncology – medical oncologist's perspective

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DÉL-PESTI CENTRUMKÓRHÁZ ORSZÁGOS HEMATOLÓGIAI ÉS INFEKTOLÓGIAI INTÉZET

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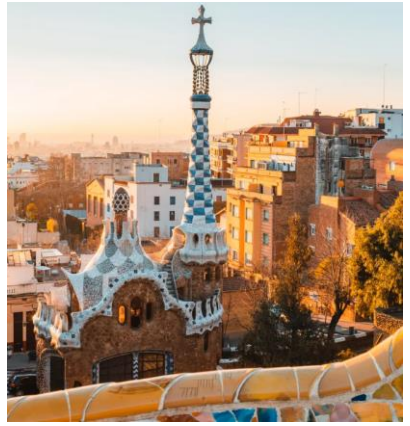
Topics

- Personalized cancer therapy – precision medicine
- Biomarkers, biomarker testing
- Types of biomarkers
- Site-agnostic cancer therapies and their biomarkers
- Basket trials
- Examples of biomarkers and related treatments
- Companion diagnostics

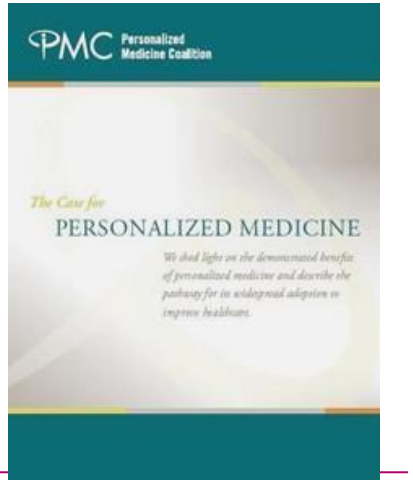


Cancer – what is it?

- Broad group of malignant diseases involving unregulated cell growth in the patient's body
- Special alteration in the genes which regulates cell growth and differentiation
- Cancer is a genetic disorder
- Different „cancer genes"
  - Oncogenes – normally promotes cell division, controll the cell cycle and apoptosis – mutated: unscheduled proliferation, genomic/chromosomal instability
  - Tumor supressor genes – normally supress cell division – mutated: fails to supress
  - DNA repair gene mutation – normally repair DNA mutations – mutated: fails to repair the DNA

Personalized cancer therapy

- Convenctionally defined cancer indications based on tumor histological findings
- Drug development entered a new era with the development of trastuzumab – treatment for metastatic, then early breast cancer
- Targeted anti-cancer drugs are approved together with a companion diagnostic (**CDx**)
- Cancers of the same histologic type consist of several molecular subgroups
- Discoveries in molecular biology and the development of targeted cancer therapies bring an important new concept:
  PERSONALIZED MEDICINE



Definition of personalized medicine

Every tumor is different
Every cancer patient is different

- A type of medical care in which treatment is customized for an individual patient
- A form of medicine that uses information about a person's own genes or proteins to prevent, diagnose, or treat disease.
- Each patient with metastatic cancer may harbor numerous genetic aberrations, and a multitude of abnormalities may be seen among patients who have the same pathologic diagnosis
- Also called **precision medicine**.
- It is a special approach to medical care in which disease prevention, diagnosis, and treatment are tailored to the genes, proteins, and other substances of a unique patient

Biomarkers

- Biomarkers are various types of molecules: proteins, hormons, genes and other substances
- Important indicator of normal or pathogenic biological processes
- Biomarkers used not only in oncology but other clinical fields (diabetes-care (HgbA1c), asthma, heart-failure (pro-BNP), other diseases…
- NCI definition: biological molecule found in blood, other bodily fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease….[and] may be used to see how well the body responds to a treatment for a disease or condition

Biomarker testing

- These markers (of solid tumors also blood, cancer) can provide information about patient's unique cancer.
- Biomarker testing may help to choose proper cancer treatment for a unique patients
- Special laboratory methods check for certain genes, protein, other molecules
- Biomarker testing for cancer treatment may also be called: ***tumor genetic testing, genomic testing or genomic profiling, molecular testing or molecular profiling, tumor subtyping***
- A biomarker test may be called a **companion diagnostic test** if it is paired with a specific treatment.
- Different from genetic testing**!!** of inherited mutations (passing from parents)

Advantages of biomarker testing

- Biomarker tests can ***help to select a cancer treatment for an unique patient***
- Some treatments (targeted therapies and immunoncological treatment) can work only for patients whose cancers have certain biomarkers
- Biomarker testing is an important part of precision medicine,
- Using biomarker testing ***to select treatments*** that are most likely to help a given patient
- Sparing patient from getting treatments that are not likely to help, ***sparing for unnecessary toxicity***
- ***Reducing the economic burden*** of expensive (and not necessary) treatments
- Ethical issues – protect the participant (confidentiality of data, IC, Scientific integrity, transparency and recognition of healt and legal risks, etc)

Single marker testing versus multigenic testing

- Several factors affect how medical oncologists use biomarkers in real-world practice
- Rutin testing: for example to test HER2 in breast cancer, KRAs in metastatic colorectal cancer, BRAF V600 mutation in metastatic melanoma
- Multigen testing: for example 58 genes, 60 genes, 160 genes testing etc.
- Next-generation sequencing (NGS) hundreds of genes can be tested - NGS can be done on blood or tumor samples (biopsy, surgery specimen, liquid biopsy) and looks at the gene signature of the cancer (FoundationOne, Oncompass, Oncomine etc.)
- The cost of next-generation sequencing has declined in recent years
- The results of NGS testing may provide an opportunity for off-label treatments

Ralf Huss, in Translational Regenerative Medicine, 2015

Paradigm-shift: site-agnostic biomarkers

- **We have some approved cancer drug that targets a key genetic driver of cancer, rather than a specific type of tumor**
- Have the potential to transform cancer treatment
- May 2017: The first tissue agnostic indications approved by the FDA were **PEMBROLIZUMAB,** for tumors with microsatellite instability-high (**MSI-H**) or mismatch repair deficient (**dMMR**) tumors
- November 2018 **LAROTRECTINIB** was approved for **NTRK gene fusion tumors** (neurotrophic tyrosine receptor kinase)
- August 2019 **ENTRECTINIB** was granted accelerated approval by FDA for adult and adolescent patients whose cancers have the specific genetic defect, **NTRK gene fusion** and for whom there are no effective treatments
- Site-agnostics biomarkers and therapies were tested in specially designed clin. trials

BASKET trials

- Increasing number of specially-designed BASKET trials in the last few years
- The **investigational drug is studied for more than one conventional cancer indication simultaneously**
- Due to the low frequency of a given molecular alteration, usually patient data from different trials were pooled to evaluate the efficacy accross the different cancer indications
- PEMROLIZUMAB agnostic treatment data –five different trials' data were pooled to prove the drug's efficacy in different cancer indications
- LAROTRECTINIB – 3 pooled trials
- Another recently published basket trial: NERATINIB – administered to patients harboring HER2 or HER3: response was found in breast cancer, biliary tract cancer, cervical cancer, lung cancer (no response to neratinib in colorectal cancer, endometrial, gastroesophageal and ovarian cancer)
- Tumor site and histology may play role in the efficacy of targeted therapy – the oncogenic drivers cannot always be used to select patients to a specific targeted cancer treatment

EXAMPLES of biomarkers and related treatments

Biomarker	Type of cancer	Therapy	Target
Estrogen receptor	Breast	Tamoxifen, aromataz inhibitors	ER
HER2 (gene amplification)	Breast, gastric, colon etc.	Trastuzumab, pertuzumab, trastuzumab-emtansine, lapatinib, neratinib etc.	HER2
EGFR (kinase)	NSCLC	Erlotinib, gefitinib	EGFR
BRCA 1/2	Breast, ovarium, pancreas, prostata etc	Olaparib, veliparib	PARP
BRAF V600E	Melanoma, colorectal	Vemurafenib tramatinib, dabrafenib, cometinib, encorafenib etc	BRAF
EGFR + KRAS (KRAS mutation)	Colorectal cancer	Cetuximab, panitumumab	EGFR, KRAS

EGFR: epidermal growt factor receptor, ALK: anaplastic lymphoma kinase, KRAS: Kirsten rat sarcoma; BRCA: breast cancer gene; PARP: poly-ADP ribose polymerase

Development of drug-diagnostics

- Ideally drug development should rely on molecular understannding of the pathophysiology and mechanism of action of the drug proband
- **Companion diagnostic assay (CDx)** is developed paralell to the drug
- In these clinical trials the molecular testing becomes an important part os patient selection.
- Before using in big clinical trials, the CDx assay must tested with regard of sensitivity, specificity, robustness and reproducibility, practicality
- It is important to avoid the false-positive and false-negative results
- Trastuzumab and the HER2 detecting assay was the first approved drug-diagnostic combination
- August 2022: 145 approved CDx

Summary - take home messages

- Drug development entered a new era
- Better understanding of tumor pathophysiology and discoveries in molecular biology lead to an important new concept: **PERSONALIZED MEDICINE**
- Biomarker testing may help to choose proper cancer treatment for a unique patients
- The cost of sequencing (also NGS) has declined in recent years
- In basket trials the investigational drug is studied for more than one conventional cancer indication simultaneously
- Companion diagnostic assay **(CDx)** is developed paralell to the drug

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Thanks for your attention!

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