Regional Center for Cancer Biomarkers

State of the art and trends of circulating cancer biomarkers: a paradigmatic example

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Where we are

A limited number of markers are recommended in a limited number of clinical scenarios for the routine use. They were discovered over 30 years ago and are associated to tumor bulk

- Tissue-specific markers (i.e. PSA, Thyroglobulin, some hormones, …)
- Onco-fetal antigens (i.e. CEA, AFP, …)
- Carbohydrate antigens (i.e. CA125, CA19-9, CA15.3. …)

Where are we going

Novel technologies

- Genomics
- Proteomics
- Multiplexing
- …..

Novel biological matrixes

- Exosoms
- Saliva
- ….

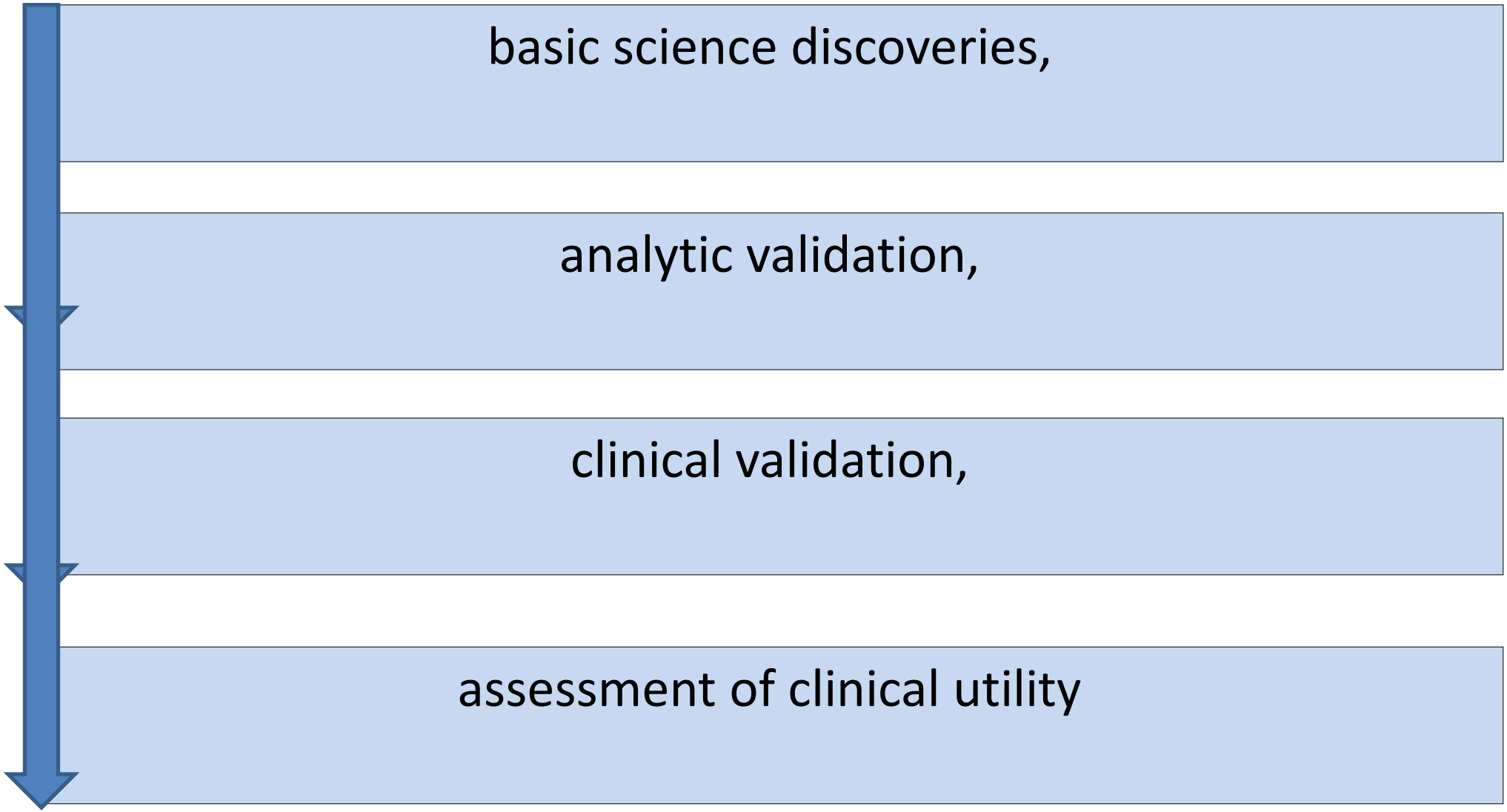
Novel biomarker classes

- Circulating nucleic acids
- Mechanism related biomarkers
- …..

Where are we going

- The challenge with biomarkers is to translate a constantly increasing complexity (biological, analytical, computational,…) into tools and decision criteria realistically transferable in a reasonable time frame to the clinical practice.

The pipeline of translational research on biomarkers can be described as a continuum, from …



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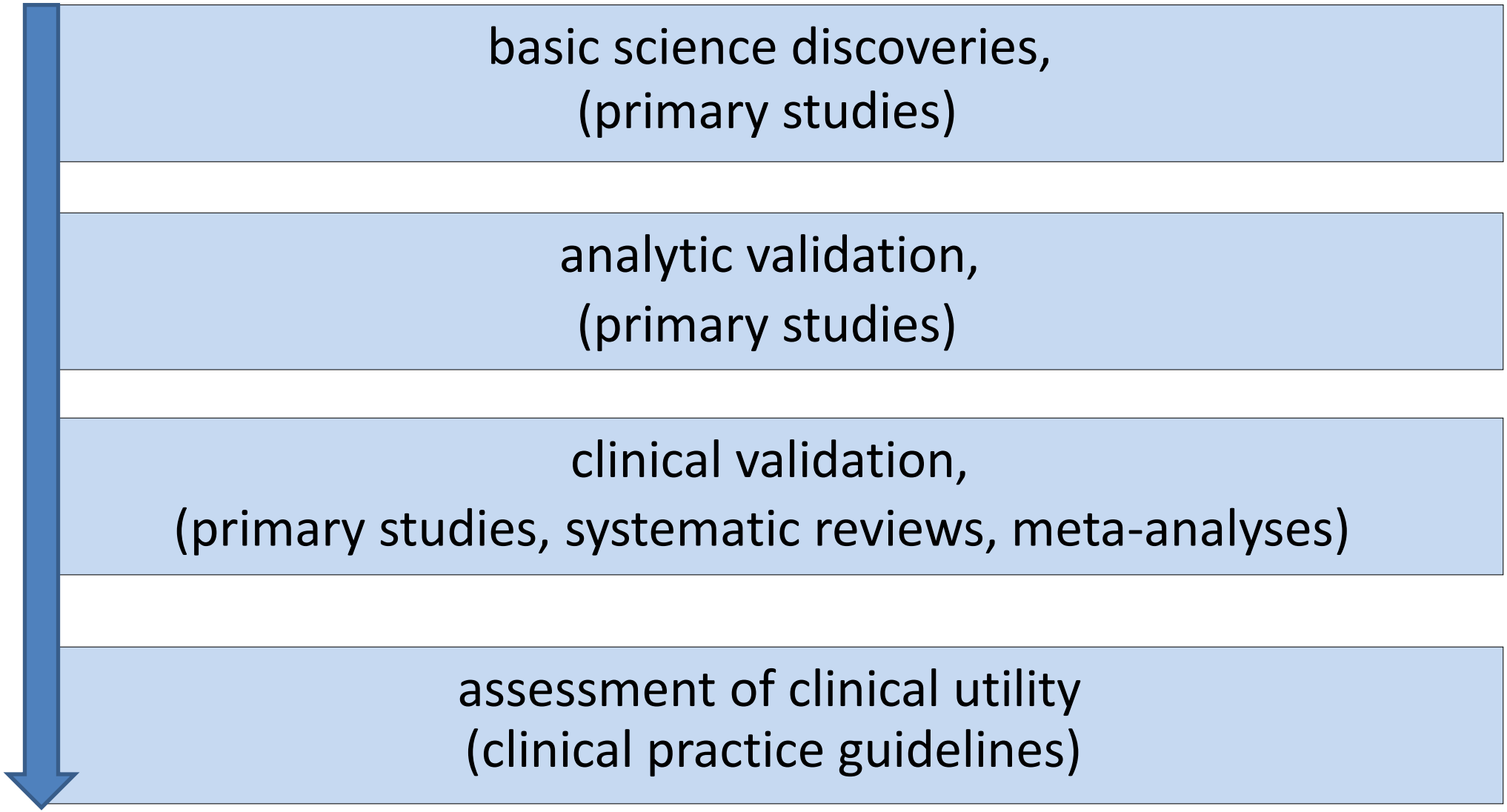

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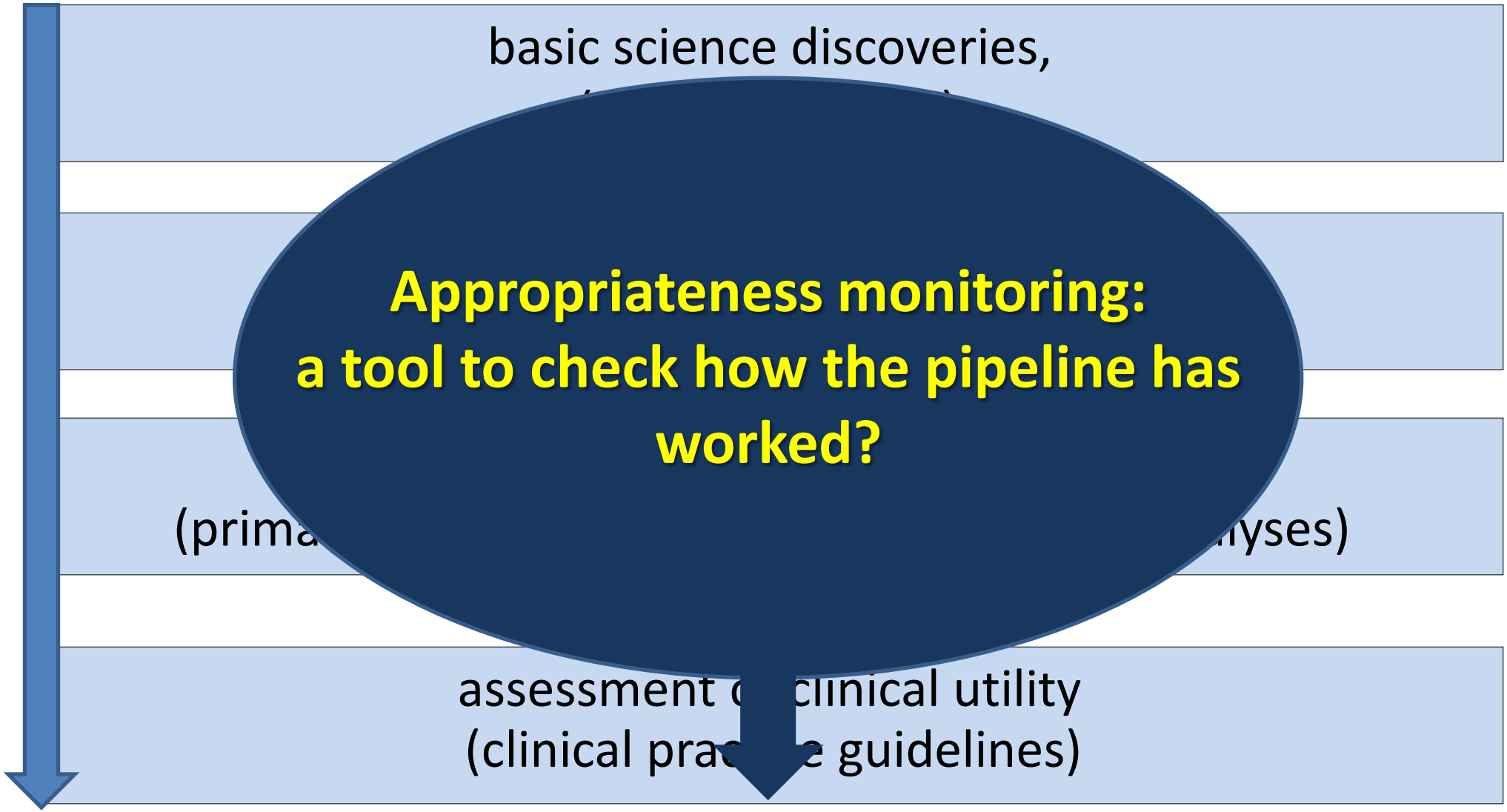

Appropriateness monitoring: a tool to check how the “pipeline” has worked?

An effective research flow should ultimately lead to an appropriate implementation of a given intervention in the clinical practice.

Circulating tumor markers are a paradigmatic example to test how results of research have been eventually translated in clinical practice.

Traditional circulating tumor markers: a valuable template for novel biomarkers?

- Since their first discovery, traditional circulating tumor markers (CEA, AFP, CA125, PSA, ...) have been evaluated in thousands of subjects and used for clinical decisions in hundred of thousands of patients, using fully standardized assay methods supervised through established quality assurance programs.
- Can they be the template for the translational research of novel biomarkers into the clinical practice ?

How appropriateness of tumor marker ordering can be appraised ?

Indicators are the basic tool to monitor appropriateness

Are there established indicators to monitor appropriateness of laboratory test ordering?

The general framework of appropriateness appraisal of laboratory testing

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Three meta-analyses are available

Toward Optimal Laboratory Use

Do We Know What Inappropriate Laboratory Utilization Is?

A Systematic Review of Laboratory Clinical Audits

Carl van Walraven, MD, MSc, FRCPC; C. David Naylor, MD, DPhil, FRCPC

JAMA. 1998;280:550-558

OPEN ACCESS Freely available online

PLOS | ONE

The Landscape of Inappropriate Laboratory Testing: A 15-Year Meta-Analysis

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Overtesting and undertesting in primary care: a systematic review and meta-analysis

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Focused on several diagnostic tests. Only 11,165 IVD orders were examined

Can general indications (i.e. indicators) be extracted from available meta-analysis ?

- The available meta-analysis examined for appropriateness 11,165 + 13,000 + 1,605,095 IVD test orders, …
  - spread over 10 different diagnostic sectors, …
  - from 1966 to 2017 (51 years)

- 4-5 billion tests per year are requested only in the United

Indicators to monitor appropriateness of tumor marker ordering are not available from the literature

clinical laboratory.

Assessment of appropriateness of requests of tumor markers – Traditional approach

- It is based on the retrospective evaluation of the requests with reference to medical records.
- Requisition forms of laboratory tests usually do not contain reliable clinical information, thus impairing a direct appraisal of appropriateness.
- Results obtained from a limited number of studies focused on particular patient series are not suitable to develop indicators to be used in the “real world”

Indicators to monitor appropriateness of tumor markers ordering

We developed “ordering rate indicators” as proxy indicators of inappropriateness using an epidemiology-based model:

Ordered tumor markers

vs.

expected orders of tumor markers according to cancer prevalence and guidelines recommendations

(Gion M, et al. Clin Chem Lab Med 2016; 54: 473-82)

Epidemiological model to estimate the rate of inappropriateness of tumor marker requests

- ***Ordered***. The type and number of tumor markers ordered to outpatients in all Italian Regions in 2011 and 2012 was obtained from the Ministry of Health (over 24 million tumor marker requests were examined).
- ***Expected***. Epidemiological data on cancer prevalence were obtained from the Italian Association of Cancer Registries (AIRTum) database (updated 2010).

(Gion M, et al. Clin Chem Lab Med 2016; 54: 473-82)

Tumor marker orders *vs* Italian resident population

Data from: Nsis - Flusso di specialistica ambulatoriale Art 50 (Legge 326/2003)

	2012
Italian resident population	59,685,227
Tumor marker orders	13,207,289
Tumor markers orders/ 1000 inhabitants	221.3

(Gion M, et al. Clin Chem Lab Med 2016; 54: 473-82)

Matching orders of tumor markers with prevalence of target malignancies

- We further explored if ordering behavior was driven by the target disease in the case of those markers recommended for specific cancer types only.

(Gion M, et al. Clin Chem Lab Med 2016; 54: 473-82)

Matching marker orders with the prevalence target malignancies

Target malignancy	Recommended marker	Prevalent cases (IT, 2010)	Expected requests	Registered requests [4]
Breast Ca.	CA15.3	522.235	432.000 [1]	**1.078.864**
Ovarian Ca.+ Endometrial Ca.	CA125	129.515	659.030 [2]	**977.189**
Pancreatic Ca. + Biliary tract Ca.	CA19.9	18.755	124.751 [3]	**1.386.169**

[1] Assumption: CA15.3 not requested in prevalent cases without evidence of disease; 12 CA15.3/year in every prevalent case with metastatic disease

[2] Assumption: 2 CA125/year in every prevalent case of ovarian or endometrial cancer; 1 CA125/year in every women with suspicious adnexal mass (~400.000)

[3] Assumption: 12 CA19.9/year in every prevalent case of Pancreatic Ca.; 1 CA19.9/year in every prevalent

[4] Italy, 2012

(Gion M, et al. Clin Chem Lab Med 2016; 54: 473-82)

- The developed proxy indicator of inappropriateness showed that tumor markers are overused in Italy and their ordering pattern is not related to cancer epidemiological figures.

DE GRUYTER

Clin Chem Lab Med 2016; 54(3): 473–482

Massimo Gion*, Lucia Peloso, Chiara Trevisiol, Elisa Squarcina, Marco Zappa and Aline S.C. Fabricio

An epidemiology-based model as a tool to monitor the outbreak of inappropriateness in tumor marker requests: a national scale study

IJBM

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DOI: 10.5301/ijbm.5000274

SHORT COMMUNICATION

Epidemiology-based assessment of tumor marker overordering in breast cancer: an algorithm to examine different disease conditions

Chiara Trevisiol[1], Massimo Gion[2], Ruggero Dittadi[3], Marco Zappa[4], Aline S.C. Fabricio[2]

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WILEY Journal of Evaluation in Clinical Practice
International Journal of Public Health Policy and Health Services Research

ORIGINAL ARTICLE

Indicators of inappropriate tumour marker use through the mining of electronic health records

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Tumor markers overuse

Consequences

- Overdiagnosis and risk of overtreatment
- Unnecessary costs
- Overloading of health care services and facilities for confirmatory tests in false positive cases

Considerations

- The pipeline of translational research on tumor markers has not been fully effective, at least in the implementation phase.

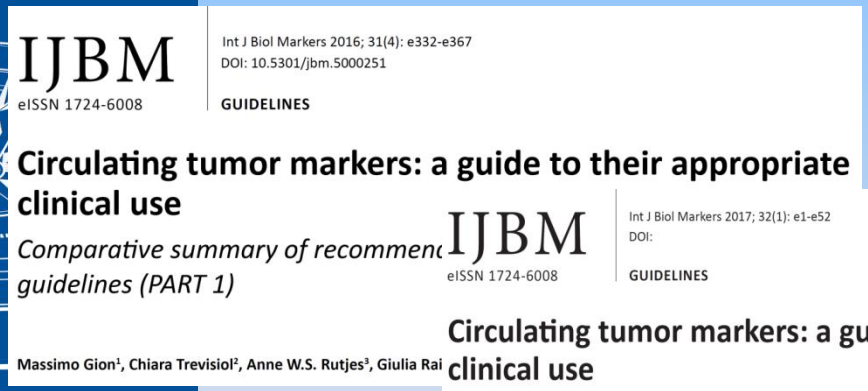
Why physicians' compliance to published recommendations on tumor markers is poor?

Clinical Practice Guidelines

Potential shortcomings limiting their implementation in clinical practice

- Quality
- Comprehensiveness
- Consistency

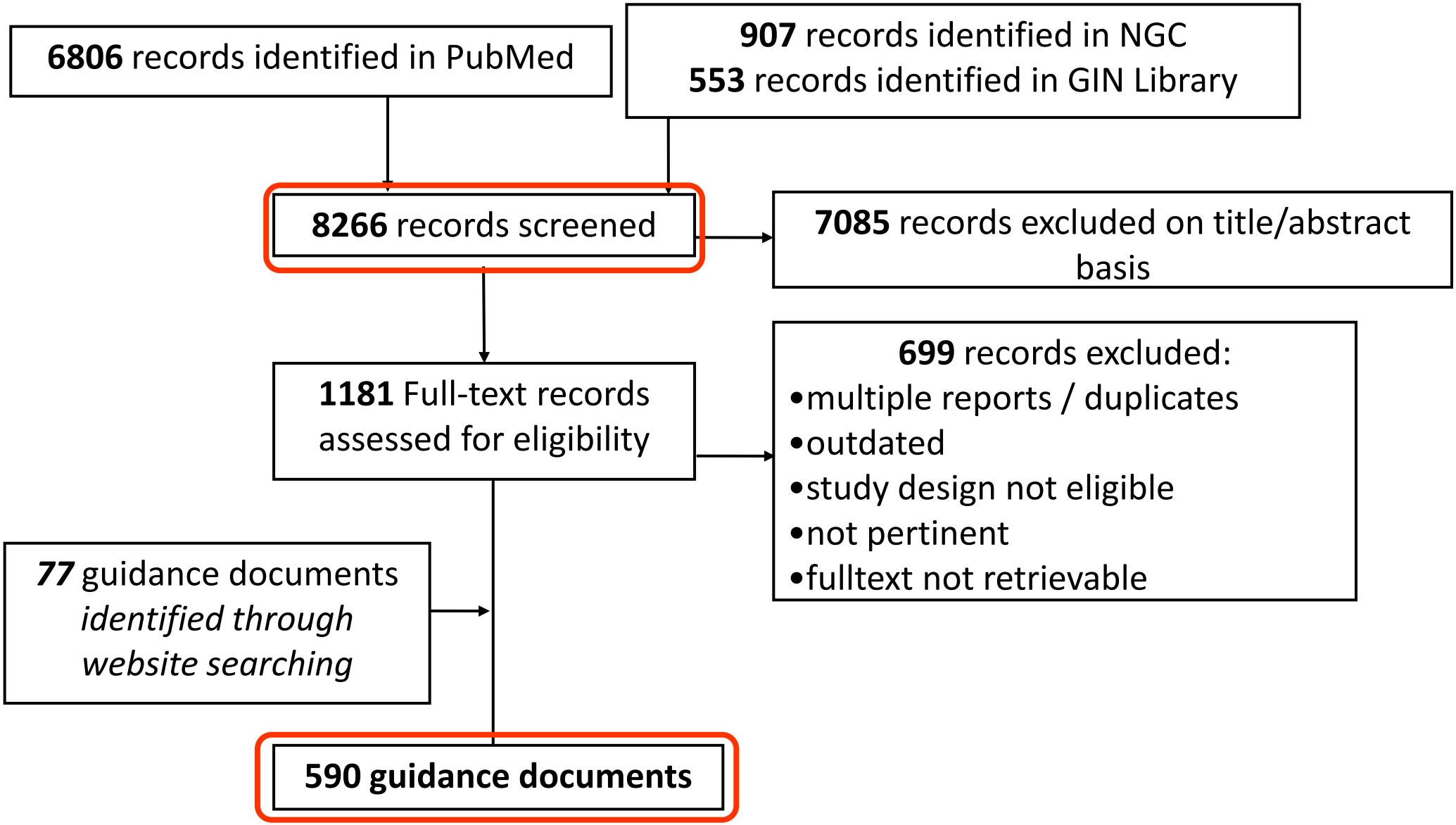
Recommendations on circulating tumor markers offered by available clinical practice guidelines on solid tumors have been summarized and side-by-side compared.



Project steps

1. Search of guidelines on solid tumors (years: 2009-2015)
2. Selection of pertinent guidelines
3. Guidelines quality assessment (IOM, AGREE)
4. Extraction of information on tumor markers
5. Summary of recommendations and information

(Gion M, Trevisiol C, Rutjes AWS, Rainato G, Fabricio ASC. Int J Biol Markers 2016; 31(4): e332-e367, 32(1): e1-e52 and 32(2): e147-e181)



(Gion M, Trevisiol C, Rutjes AWS, Rainato G, Fabricio ASC. Int J Biol Markers 2016; 31(4): e332-e367, 32(1): e1-e52 and 32(2): e147-e181)

Guidelines quality

Selected guidance documents were first appraised to determine their adherence to the **Institute of Medicine (IOM)** standard:

An explicit statement (and evidences) that the clinical practice guideline was based on a systematic review

(Gion M, Trevisiol C, Rutjes AWS, Rainato G, Fabricio ASC. Int J Biol Markers 2016; 31(4): e332-e367, 32(1): e1-e52 and 32(2): e147-e181)

Adherence of guidance documents reported as "Clinical Practice Guidelines" to the IOM standard

• **Total**	**590 (100%)**
• **Based on systematic reviews of existing evidence (CPGs)**	**168 (28.5%)**
• **Systematic search declared, but applied methods did not meet minimum standards for quality**	**137 (23.2%)**
• **Guidance documents did not report any use of literature evaluation**	**164 (27.8%)**

(Gion M, Trevisiol C, Rutjes AWS, Rainato G, Fabricio ASC. Int J Biol Markers 2016; 31(4): e332-e367, 32(1): e1-e52 and 32(2): e147-e181)

Insufficient uptake of systematic search methods in clinical practice guideline: a systematic review

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Submitted

Guidelines quality

- A relatively small number of guidance documents was informed by scientific evidence identified through adequate systematic search methods.
- A substantial room for improvement of applied methods and reporting was observed, which could eventually impact on implementation of recommendations.

Clinical Practice Guidelines

Potential shortcoming restraining their implementation in daily practice

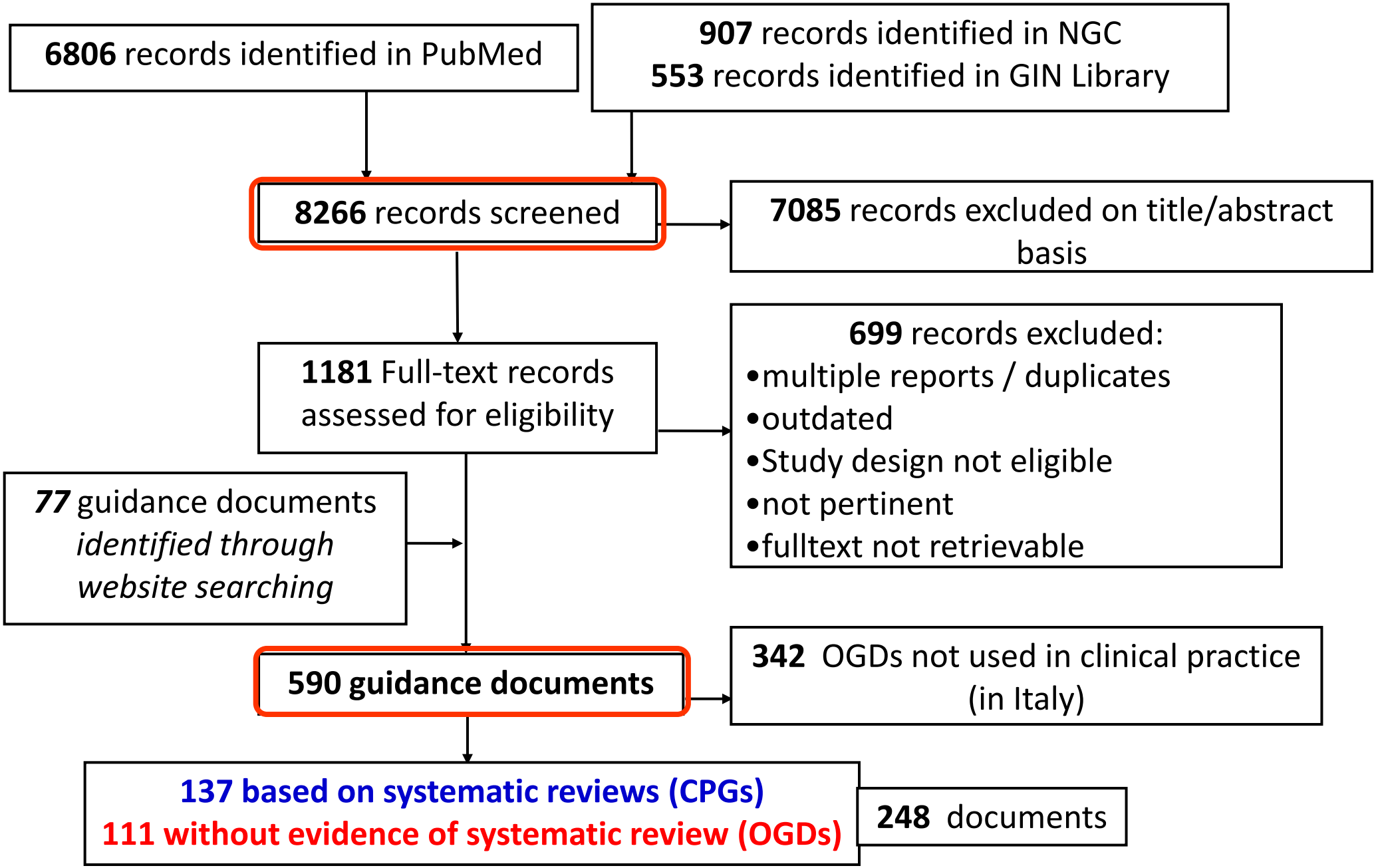
- Quality
- Comprehensiveness
- Consistency

Summary of reccomendations vs. guidelines quality

1. Documents providing evidence of systematic review (**C**linical **P**ractice **G**uidelines - **CPGs**).
2. Guidance documents without evidence of systematic review (**O**ther **G**uidance **D**ocuments - **OGDs**).

- **OGDs** are produced also by authoritative institutions or medical societies (and are widely used).
- Whenever 25% or more of the panel members declared that a given **OGD** was used in clinical practice, it was retained.

(Gion M, Trevisiol C, Rutjes AWS, Rainato G, Fabricio ASC. Int J Biol Markers 2016; 31(4): e332-e367, 32(1): e1-e52 and 32(2): e147-e181)



(Gion M, Trevisiol C, Rutjes AWS, Rainato G, Fabricio ASC. Int J Biol Markers 2016; 31(4): e332-e367, 32(1): e1-e52 and 32(2): e147-e181)

Summary of Guidelines reccomendations

Comprehensiveness

- Do available recommendations meet the majority of clinical questions?

Consistency

- Are recommendations on a same question consistent among different guidelines?

Gidelines comprehensivenes and consistency

Gastrointestinal tract malignancies as an example

Legenda

CEA: the marker is recommended

None/No CA19.9: guidelines explicitly recommend against the use of any marker/a given marker

n.c.: scenario not considered by guidelines

∅ : (empty set symbol) the examined guidelines either do not address TMs or, if TMs are addressed, do not formulate recommendations

Recommendations (both formal and implicit) from CPGs and from OGDs

Scenario \ Cancer type	Colorectal	Esophageal	Hepatocarcinoma	Pancreatic	Gastric	Biliary tract
Screening	∅ (*)	∅	AFP/∅ (*) No AFP PIVKA, AFPL3 yes/no	n.c. ∅	∅	∅ (*) None/CA19.9
Differential diagnosis	∅ No CA19.9	∅	∅ AFP yes/no, AFPL3	∅ CA19.9	∅ CA19.9, CEA	∅ None/CA19.9
Initial work-up	CEA/∅	∅	∅ AFP	CA19.9/∅	∅	∅ CA19.9, CEA
Reassessment after curative treatment	∅	n.c.	n.c. AFP/∅	n.c. CA19.9	n.c. CA19.9, CEA/∅	n.c. ∅
Follow-up	CEA No CA19.9	∅	AFP	n.c. CA19.9	None	n.c. ∅
Monitoring treatment response (advanced disease)	∅	∅	∅ AFP	∅ CA19.9	∅	n.c. CA19.9, CEA/∅

(*) Screening of people at increased risk

Recommendations (both formal and implicit) from CPGs and from OGDs

Scenario \ Cancer type	Colorectal	Esophageal	Hepatocarcinoma	Pancreatic	Gastric	Biliary tract
Screening		∅		∅	∅	
Differential diagnosis						
Initial work-up		∅			∅	
Reassessment after curative treatment	∅					∅
Follow-up		∅				∅
Monitoring treatment response (advanced disease)	∅	∅			∅	

Unmet clinical questions

(*) Screening of people at increased risk

Recommendations (both formal and implicit) from CPGs and from OGDs

Inconsistencies among different guidelines

Cancer type / Scenario	Colorectal	Esophageal	Hepatocarcinoma	Pancreatic	Gastric	Biliary tract
Screening			AFP/∅ (*) ⚠ No AFP PIVKA, AFPL3 yes/no			∅ (*) ⚠ None/CA19.9
Differential diagnosis			∅ ⚠ es/no, AFPL3	∅ ⚠ CA19.9	∅ ⚠ CA19.9, CEA	∅ ⚠ None/CA19.9
Initial work-up	CEA/∅ ⚠		⚠ AFP	CA19.9/∅ ⚠		∅ ⚠ CA19.9, CEA
Reassessment after curative treatment			AFP/∅ ⚠		n.c. ⚠ CEA/∅	
Follow-up						
Monitoring treatment response (advanced disease)			∅ ⚠ AFP	∅ ⚠ CA19.9		CA19.9, CEA/∅

(*) Screening of people at increased risk

Gidelines comprehensivenes and consistency

Why available guidelines recommendations fail to meet several clinical questions on tumor marker ?

Why recommendations from different guidelines are not consistent on the same clinical question?

Requisites for adoption of a biomarker in the clinical care

Three semantic terms have been accepted as *re*quisites for adoption of a tumor marker test into clinical care:

- Analytical validity
- Clinical validity
- Clinical utility

Analytical Validity

- Analytic validity refers to the accuracy with which a particular genetic or biochemical indicator, is identified by a given laboratory test.
- It includes the specific technical requirements of the assay chosen and its performances (i.e. analytical sensitivity, specificity, ...)

Clinical Validity

- Clinical validity describes the accuracy with which a test is associated to a particular clinical condition (diagnostic sensitivity, specificity, positive and negative predictive value) or predicts a clinical outcome (prognosis, the response to a drug).

Clinical Utility

- Clinical utility refers to the risks and benefits resulting from use of the test.
- Measurement of clinical utility requires evaluation of the medical and social outcomes associated with testing, and subsequent interventions for people with both positive and negative test results.

Analytical & Clinical Validity *vs.* Clinical Utility

- Clinical utility implies that high levels of evidence exist to support the claim that the use of the tumor marker produces better outcomes for the patient than if it were not available.
- One cannot have clinical utility without high analytical and clinical validity, but ….
- … analytical and clinical validity alone are insufficient to introduce the test into routine practice.

Clinical Practice Guidelines

Frequently, guidelines do not endorse the results of research studies, because …

… Clinical Practice Guidelines cannot recommend on the basis of clinical validity alone.

The role (responsability?) of the regulatory framework

The regulatory issues (USA)

- The regulatory environment of laboratory assays, including tumor biomarker tests, is at best inconsistent.
- While the Office of In Vitro Diagnostics is superb in assessing the analytical validity of tumor biomarker tests, their hands are tied in regards to insisting on clinical utility as a criterion for clearance or approval of a tumor biomarker test.
- Therefore, approval of a tumor biomarker test by the FDA does not necessarily imply that it should be used to direct patient care.

(Hayes DF, JAMA, 2017)

The regulatory issues (EU)

- Innovative medicinal products receive a marketing authorization from the European Commission based on a positive benefit–risk assessment by the EMA.
- IVD may be sold in the EU with a CE mark after assessment and approval from a notified bodies (NB). For IVD the certification will focus on the technical features and technical quality of the products.

(Enzmann H et al, 2016)

The regulatory issues

Still a deregulated environment, as concerns cancer biomarkers!

Concluding remarks

- The clinical use of classical tumor marker is largely inappropriate, due at least in part to the scarcity of evidence on their clinical utility.
- A re-engineering of clinical research is necessary to facilitate the efficient translation of new biomarker assays in clinical practice.
- Such re-engineered research would use novel study designs based on clinical utility endpoints, whether in formal trials or in real-world studies.

Thank you for your attention

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