



*Imaging Biomarkers in Radiation Oncology and Beyond:  
Development, Evaluation and Clinical Translation*

# Imaging Biomarker Roadmap for Cancer

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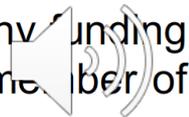
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**DISCLOSURES & CONFLICT OF INTEREST.** John Waterton holds stock in Quantitative Imaging Ltd and receives compensation from Bioxydyn Ltd, a for-profit company engaged in the discovery, development, provision and marketing of imaging biomarkers.

### Speaker Presentations - Funding Support, Disclosures, and Conflict of Interest Statement

Speakers **ARE REQUIRED** to include a slide in their PowerPoint presentation disclosing any funding support, disclosures, and conflicts of interest. The conflict may pertain to themselves, a member of their team, or an immediate family member.



# BEST resource (2016)

## Biomarker:

A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.

Molecular, histologic, radiographic or physiologic characteristics are types of biomarkers.

A biomarker is not an assessment of how an individual feels, functions, or survives.

Categories of biomarkers include:

- susceptibility/risk biomarker
- diagnostic biomarker
- monitoring biomarker
- prognostic biomarker
- predictive biomarker
- pharmacodynamic/response biomarker
- safety biomarker



BEST (Biomarkers, EndpointS, and other Tools) Resource

Authors

FDA-NIH Biomarker Working Group.

Silver Spring (MD): Food and Drug Administration (US); Bethesda (MD):

*Development of 1999 workshop  
(Atkinson et al 2001)*





Metrology definition	Colloquial definition	Examples
Ordered categorical (incl. binary)	How ugly?	
Extensive	How big?	
Intensive	How hot?	



Metrology definition	Colloquial definition	Examples
Ordered categorical (incl. binary)	How ugly?	<ul style="list-style-type: none"> <li>• TNM stage PET SPECT vis XR/CT MR us</li> <li>• OR PET SPECT vis XR/CT MR us</li> <li>• ACR BIRADS breast morphology XR</li> <li>• <sup>99m</sup>Tc-etafolatide FR+ SPECT</li> <li>• Radiomic signature of heterogeneity CT</li> </ul>
Extensive	How big?	<ul style="list-style-type: none"> <li>• LVEF SPECT MR us</li> <li>• Spleen volume CT MR</li> <li>• circumferential resection margin in rectal cancer MR</li> </ul>
Intensive	How hot?	<ul style="list-style-type: none"> <li>• <math>SUV_{max}^{111In}</math>-pentetate SPECT</li> <li>• <math>SUV_{max}^{18F}</math>-fludeoxyglucose PET</li> <li>• Aprepitant receptor occupancy % PET</li> <li>• <math>\Delta K^{trans}</math> gadoterate MR</li> <li>• DCE-US AUC us</li> <li>• MRI ADC MR</li> <li>• <sup>13</sup>C-pyruvate <math>k_p</math> MR</li> </ul>



# Problem statement: imaging biomarkers in cancer

- Not a new idea – predates molecular biology!
  - Tumour size: 1940s/50s
  - Tumor  $T_1$  (1971) led to invention of MRI
  - Exemplified in FDA/NIH biomarker workshop (1999)
- Today used routinely – all BEST categories
  - Cancer drug development
  - Regulatory approval
  - Routine oncologic practice
- Many investigational imaging biomarkers in cancer
  - Disappointing rate of translation – why?



# “...molecular, histologic, radiographic, or physiologic characteristics...”

## Biospecimen removed from patient

molecule or cell analyte detected with *in vitro* Diagnostic Device

genetics  
soluble biomarkers  
immunohistochemistry  
in situ hybridisation  
genomics  
proteomics  
metabolomics  
cytology  
microbiology  
erythrocyte sedimentation  
etc

### biofluids

urine  
blood  
exhale  
sputum  
saliva  
semen  
faeces  
synovial fluid  
CSF  
etc



### solid tissues

cervical smear  
skin biopsy  
hair follicle  
buccal biopsy  
liver biopsy  
bone biopsy  
synovial biopsy  
tumour biopsy  
excised tumour  
etc



## Biosignal measured in vivo

signals detected by *in vivo* Diagnostic Device

### electromagnetic fields & photons

PET  
SPECT  
CT, XR  
endoscopy  
fluorescence  
MRI/S  
ECG  
EEG  
MEG  
etc



### sound & pressure

ultrasound  
infrasound  
palpation  
auscultation  
plethysmography  
spirometry  
etc

imaging  
electrophysiology  
physiologic measurement  
wearables/smartphones  
etc



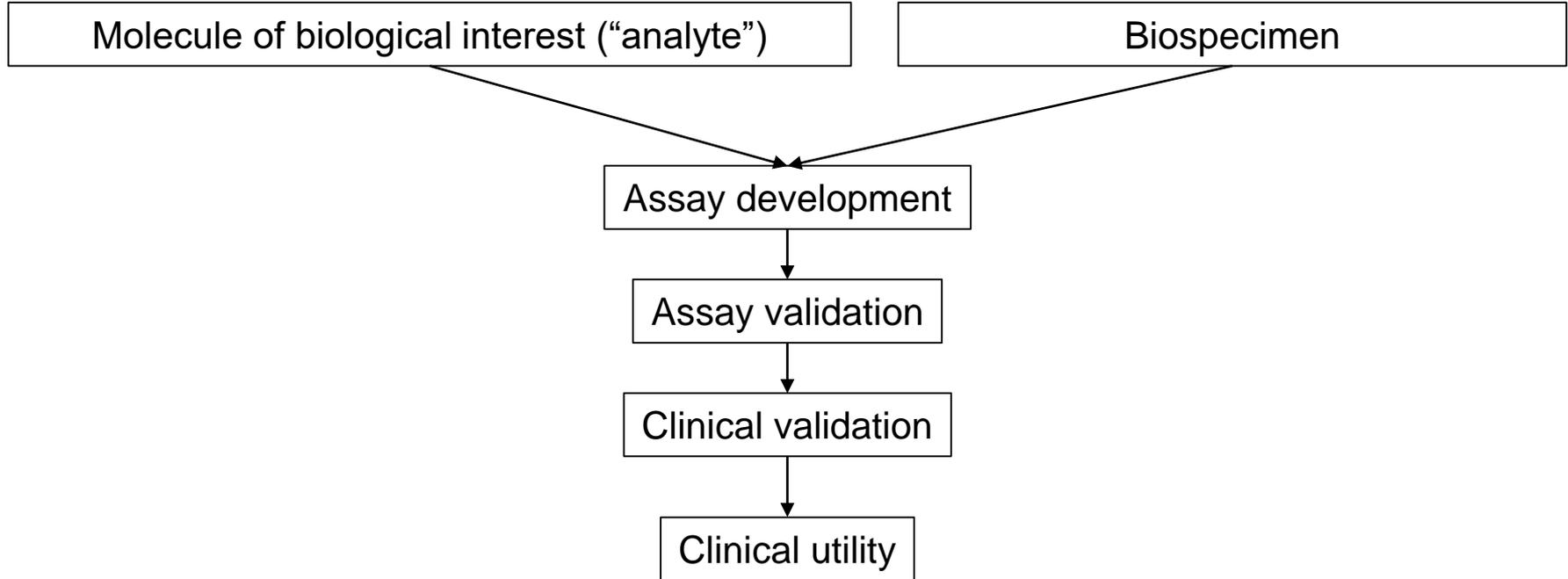
**Imaging biomarker:  
Scanner in hospital Radiology Dept**

**Biospecimen biomarker:  
In vitro diagnostic device**

Different scanners from different vendors installed in different hospitals	Identical IVDDs
Scanners not designed, maintained or approved for measuring biomarkers	IVDDs designed, maintained and approved for specific measurement
Main job role not quantitation	Trained, dedicated staff
Quality depends mainly on events at the moment of scanning	Quality depends mainly on the central lab
Picture quality drives innovation: unpredictable effect on quantitation	Stable platform due to regulatory approval
Seldom defined analytes	Defined molecular entity via analytical biochemistry



# Typical biospecimen biomarker validation roadmap



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<http://dx.doi.org/10.1038/nrclinonc.2016.162>

Includes supplementary files

- Problem statement
- Examples – all modalities and contexts of use
- Definitions
- Detailed roadmap
- Recommendations

OPEN

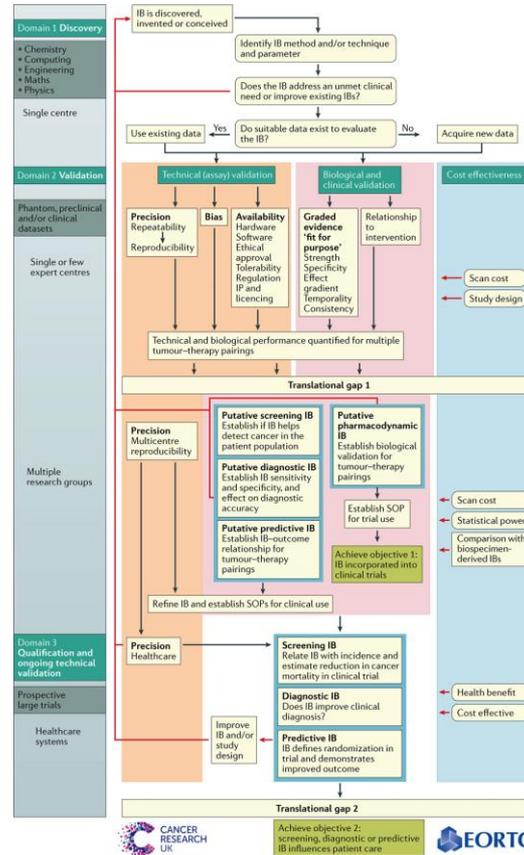
## Imaging biomarker roadmap for cancer studies

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Abstract | Imaging biomarkers (IBs) are integral to the routine management of patients with cancer. IBs used daily in oncology include clinical TNM stage, objective response and left ventricular ejection fraction. Other CT, MRI, PET and ultrasonography biomarkers are used



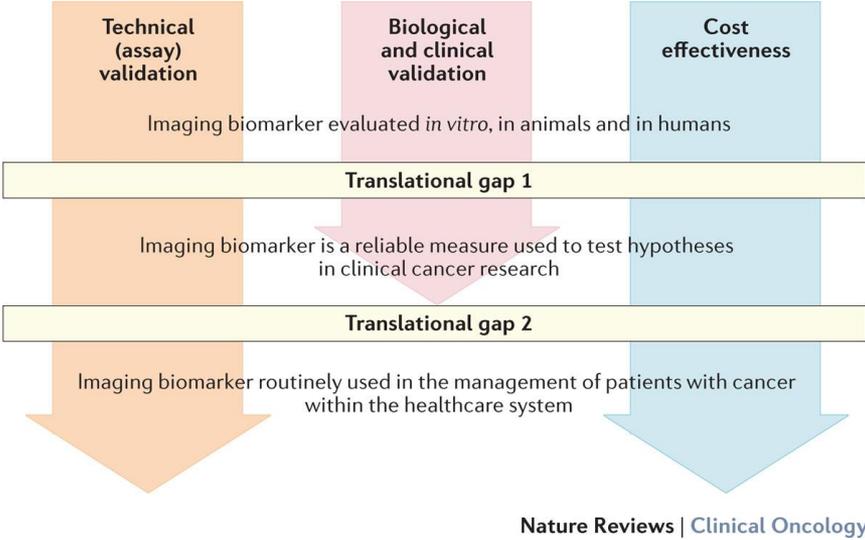
**Figure 2** The imaging biomarker roadmap



Nature Reviews | Clinical Oncology



**Figure 1** Overview of the imaging biomarker roadmap



O'Connor, J. P. B. *et al.* (2016) Imaging biomarker roadmap for cancer studies  
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# Key perspectives

	Imaging (biosignal) bm	Typical biospecimen bm
Technical validation, clinical validation, clinical utility	Iterative in parallel	Mainly in series
Biological and clinical validity	Biological validation platform of evidence e.g. Bradford Hill criteria	Definitive clinical outcome studies e.g. Kaplan Meier

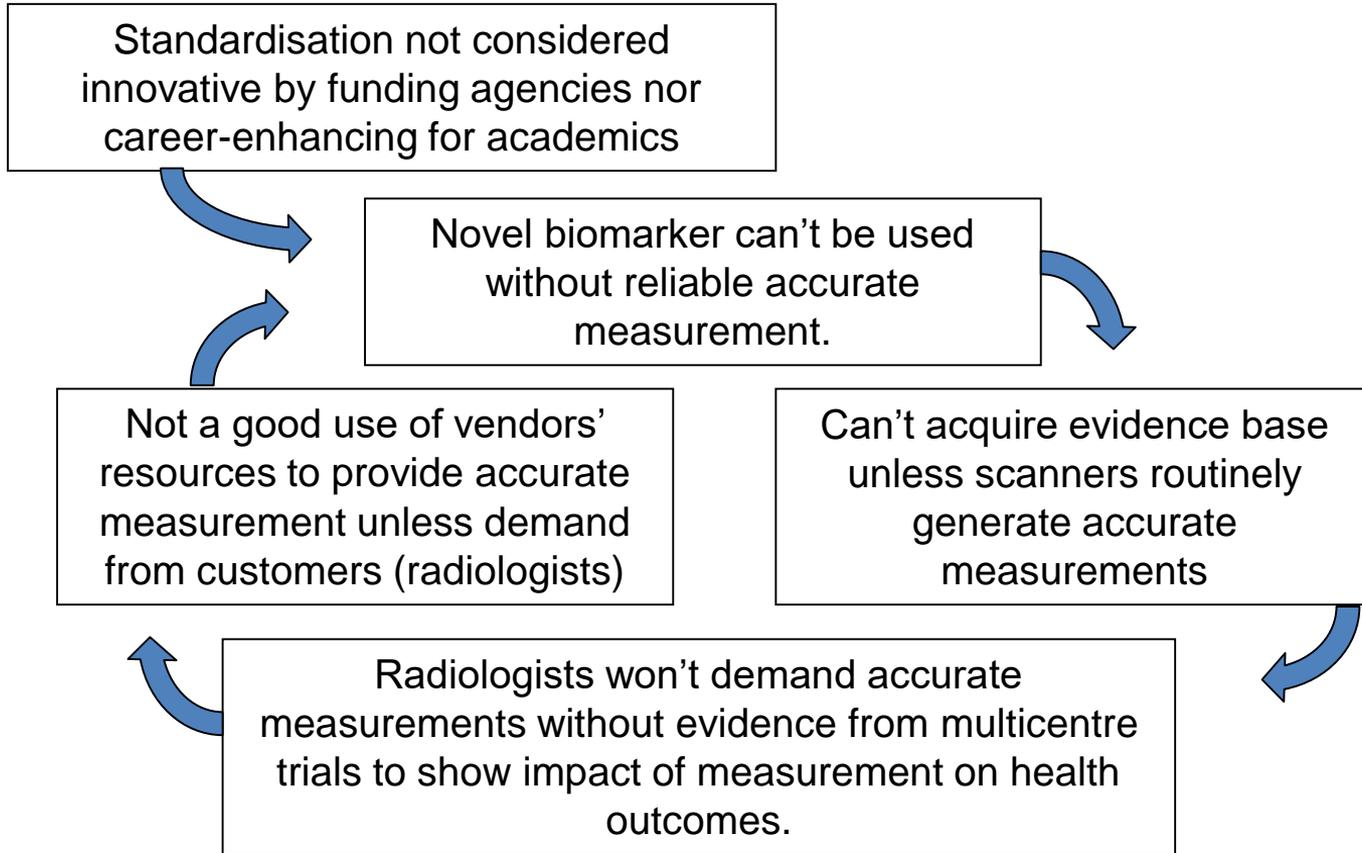


# Roadmap recommendations

1. Align grants and publications to roadmap
2. Exhaustively document methodology in publications
- 3-7. Technical (assay validation)
  - Consensus, accreditation, repeatability, reproducibility, analysis methodology
- 8-11. Biological and clinical validation
  - Platform of evidence (Bradford Hill criteria)
  - Imaging-pathology correlation (human and animal)
  - Data sharing
  - Publication bias
12. Design of outcome studies
- 13-14. Cost effectiveness and clinical utility
  - Imaging agents pricing; QALY advantage



# The problem of poorly aligned incentives



# Innovative approaches to incentivisation

Incentivisation through public-private partnerships, professional bodies

- Standardising FDG-PET, FLT-PET, MRI-ADC, MRI- $K^{trans}$ , MRI-DIILD etc



Academics innovate, businesses standardise



