

## **Advances in Imaging Biomarkers: Innovative Technologies, Applications in R&D and Clinical Practice, Informatics and Regulatory Requirements**

This report discusses advances in key technologies, the use of imaging biomarkers in drug discovery, as well as development and current use in clinical practice. It also outlines key collaborative initiatives in standardizing imaging technologies and informatics, as well as improving quantification and qualification without which the vision will not be realized.

### **Scope**

- Highlights key technologies for imaging biomarker development in various research and clinical settings, as well as pivotal technology developments.
- Analyzes imaging biomarkers currently used in clinical practice as well as the future of imaging biomarkers.
- Provides case studies of individual imaging biomarkers and the companies/research collaborations responsible for their development.
- Discusses key collaborative initiatives aiming to introduce standards and improve quantification of imaging biomarkers.
- Analyzes potential for cost savings from the use of imaging biomarkers.

### **Research and analysis highlights**

Imaging biomarkers are attractive & are now widely used in drug discovery development & in clinical care. Imaging biomarkers provide non-invasive approaches that are translatable from the laboratory to the clinic & allow researchers & clinicians to see in great detail how drugs are behaving in vivo.

Small animal imaging is a rapidly growing area in the preclinical development of new pharmaceuticals. Instrumentation to allow CT, PET, SPECT, MRI, ultrasound or optical imaging of small animals is available from a large number of suppliers & the largest pharma companies are actively developing their capabilities in this area.

The use of imaging biomarkers in clinical medicine has the potential to change the standard of care in many disease states for example by providing the ability to find tumors more easily & to stratify them according to the most appropriate therapy type. Molecular imaging can also identify other lesions, such as amyloid deposits

### **Key reasons to purchase this research**

- Identify key technologies for development of imaging biomarkers to assist in biomarker discovery & development
- Identify relevance of imaging biomarkers to drug discovery & development
- Learn about the important efforts of public-private consortia that are working to develop new imaging biomarkers, qualify existing imaging biomarkers
- Understand potential for imaging biomarkers to improve diagnostic processes, enabling earlier disease identification & promoting preventive medicine
- Discover the potential of imaging biomarkers for improving decision making, terminating unsuitable drug projects & reducing costs in clinical care

# Table of Contents

## Advances in Imaging Biomarkers

Executive summary 10

Introduction 10

Imaging biomarkers: discovery, development & supporting technologies 11

R&D applications of imaging biomarkers 12

Clinical applications of imaging biomarkers 13

Informatics supporting the clinical application of imaging biomarkers 14

Imaging centers 15

Validation, qualification and regulation of imaging biomarkers 16

The future of the imaging biomarker market 17

Chapter 1 Introduction 20

Summary 20

Introduction 21

Overview of imaging modalities 21

Imaging biomarkers in research and clinical practice 26

Prognostic imaging biomarkers 28

Imaging biomarkers of response 28

Imaging biomarkers of efficacy and dosing 29

Imaging biomarkers of safety 30

Therapeutic areas 30

Importance of imaging biomarkers 30

Report outline 32

Chapter 2 Imaging biomarkers: discovery, development & supporting technologies 34

Summary 34

Discovering and developing new imaging biomarkers 35

Advances in imaging technologies and molecular probes 37

Molecular imaging probes 38

NIH-sponsored projects driving molecular imaging 39

Accessibility of molecular imaging probes for PET imaging 40

Combined imaging modalities 42

Technical advances in the field of MRI 43

High field MRI 43

Functional MRI 43

Magnetic resonance spectroscopy 44

Diffusion weighted MRI 45

Targeted probes for MRI 46

Improving MRI resolution with hyperpolarization 46

Spectral CT 50

Advances in optical imaging 51

Photoacoustic imaging 51

Conclusions 52

Chapter 3 R&D applications of imaging biomarkers 54

Summary 54

Introduction 55

Imaging biomarkers in drug discovery 56

Imaging biomarkers in preclinical development 57

Molecular imaging in preclinical development 58  
Imaging toxicity in the preclinical setting 60  
Preclinical optical imaging 61  
Imaging biomarkers in clinical drug development 61  
Imaging biomarkers in Phase 0 clinical studies 62  
Imaging biomarkers in Phase I and II clinical trials 63  
Imaging in late stage clinical trials 64  
Imaging in clinical studies in oncology 65  
Imaging biomarkers in clinical studies of CNS therapeutics 65  
Imaging in cardiovascular clinical trials 66  
Pharma's imaging centers 67  
Case study: the GlaxoSmithKline Clinical Imaging Centre 67  
Case study: imaging biomarker development at AstraZeneca 68  
Contract research organizations for imaging clinical trials 68  
The Society for Nuclear Medicine's Clinical Trials Network 69  
Pre-competitive consortia developing imaging biomarkers 70  
The Biomarkers Consortium 71  
Conclusion 74  
Chapter 4 Clinical applications of imaging biomarkers 78  
Summary 78  
Introduction 79  
Imaging biomarkers in clinical practice: oncology 81  
Breast cancer screening with mammography 81  
Established imaging biomarkers for oncology 82  
Molecular imaging biomarkers for cancer diagnosis, prognosis and treatment monitoring 83  
Molecular imaging for HER-2 screening and treatment response 87  
18F-HX4 (Siemens) 88  
18F-ML-10 (Aposense) 89  
Cell>Point imaging biomarkers for SPECT 91  
Collaborative efforts to develop novel imaging biomarkers at the  
Centre for Translational Molecular Medicine 92  
Case study: the Cancer Imaging Program, National Cancer Institute 93  
Future growth in MRI-based diagnostic imaging biomarkers 94  
Imaging biomarkers in clinical practice: neurology 95  
Imaging biomarkers for Alzheimer's disease diagnosis and treatment monitoring 96  
The Alzheimer's Disease Neuroimaging Initiative (ADNI) 96  
Commercial PET ligands in development for AD diagnosis 98  
Imaging biomarkers for Parkinson's disease 102  
Imaging biomarkers in clinical practice: cardiovascular disease 104  
AdreView (123I-lobenguane); GE Healthcare 106  
KI-0002: Kereos 108  
BMS747158; Lantheus Medical Imaging 109  
CardioPET, BFPET and VasoPET; FluoroPharma 110  
ThromboView (Agen Biomedical) 112  
Imaging biomarkers in clinical practice: metabolic disorders 113  
Conclusion 113  
Chapter 5 Informatics supporting the clinical application of imaging biomarkers 116  
Summary 116  
Software innovation improving the discovery of imaging biomarkers 117

Pattern recognition and image analysis	117
Management of digital images	120
Medical imaging informatics and networking	120
Teleradiology	121
Conclusion	122
Chapter 6 Imaging centers	126
Summary	126
Imaging centers	127
Imaging in the US	128
Quality	129
Appropriateness	129
Reimbursement	130
Imaging in the UK	131
Imaging in India	134
Accessibility of radiopharmaceuticals	135
PET	135
SPECT	136
Conclusions	137
Chapter 7 Validation, qualification and regulation of imaging biomarkers	140
Summary	140
Introduction	141
Image quantification and standards	143
The Quantitative Imaging Biomarkers Alliance	144
Imaging biomarker qualification	146
Drug-diagnostic co-development	150
Regulatory guidelines for developing novel molecular imaging agents	150
Case study: 18F-labeled sodium fluoride	152
Conclusions	153
Chapter 8 The future of the imaging biomarker market	156
Summary	156
Introduction	157
Trends in the use of imaging biomarkers in R&D	158
Imaging clinical trials in drug development	158
Saving costs	161
The future: imaging biomarkers and companion diagnostics	162
Trends in the clinical use of imaging biomarkers	164
Prevention and prediction	164
Radiation exposure	165
Costs and reimbursement	167
Imaging biomarker market	170
Overall conclusion	174
Appendices	175
Primary research methodology	175
Glossary	175
Acknowledgements	181
Index	182
Bibliography & Endnotes	184

## List of Figures

Figure 1.1: Imaging techniques and their uses	22
Figure 1.2: Imaging biomarkers in drug development and clinical care	27
Figure 1.3: Types of biomarker and their uses in drug development and disease management	28
Figure 1.4: The potential of imaging biomarkers	31
Figure 2.5: Examples of imaging biomarkers in oncology	35
Figure 2.6: Steps in biomarker development	36
Figure 2.7: Functional magnetic resonance imaging of the brain	44
Figure 2.8: Diffusion MRI - CNS	46
Figure 2.9: Images of the lungs with conventional MRI and hyperpolarized gas MRI	48
Figure 2.10: Schematic of Spectral CT technology	50
Figure 3.11: Pharma industry productivity decline, 2000-2009	55
Figure 3.12: Uses of imaging in preclinical drug development	59
Figure 3.13: Areas of interest for the Society for Nuclear Medicine's Clinical Trials Network	70
Figure 3.14: The 'learn and confirm' model of drug discovery and development	74
Figure 4.15: Imaging modalities for biomarker detection in oncology, neurology and cardiology	80
Figure 4.16: Chemical structure of <sup>18</sup> F-ML-10 (Aposense)	89
Figure 4.17: Structures of PET ligands for Alzheimer's disease diagnosis	100
Figure 4.18: Structures of norepinephrine and AdreView	106
Figure 4.19: Results of the primary endpoint in the ADMIRE-HF study of AdreView (GE Healthcare)	108
Figure 4.20: Kereos' targeted nanoparticles	109
Figure 4.21: PET images obtained during the Phase I study of CardioPET (FluoroPharma)	112
Figure 6.22: Impact analysis of the CMS 2010 Physician Fee Schedule Final Rule Summary on global imaging payments	131
Figure 6.23: CT, MRI and radio-isotope procedures carried out in the UK annually	132
Figure 6.24: Locations of static PET scanners in the UK	133
Figure 6.25: Commercial delivery of <sup>18</sup> FDG in the British Isles	134
Figure 7.26: Evolution of biomarkers: towards clinical utility	142
Figure 7.27: Imaging biomarker qualification	146
Figure 7.28: 'Fit-for-purpose' qualification of biomarkers	147
Figure 7.29: Pilot biomarker qualification process	149
Figure 8.30: Key stakeholders in the development and use of imaging biomarkers	157
Figure 8.31: Key factors in the shift towards preventive and predictive medicine	165
Figure 8.32: Costs related to imaging equipment	168
Figure 8.33: Imaging biomarkers: lower cost and less invasive than biopsy	168
Figure 8.34: Drivers and resistors for the imaging biomarker market	171
Figure 8.35: Drivers for growth in healthcare markets in emerging economies	173
Figure 8.36: Government healthcare stimulus plans in emerging economies	173

### List of Tables

Table 1.1: Common PET positron-emitting tracer isotopes	23
Table 1.2: Common SPECT radionuclides	24
Table 1.3: Advantages and disadvantages of different imaging modalities	26
Table 2.4: Desirable characteristics of molecular imaging probes	39
Table 2.5: Academic laboratories researching hyperpolarization in MRI	49
Table 3.6: Advantages of molecular imaging of whole animals for preclinical studies	58
Table 3.7: Partners of the Biomarker Consortium	72
Table 3.8: Imaging biomarker projects being carried out by the Biomarkers Consortium	73

Table 4.9: Examples of commercial developmental molecular imaging biomarkers in oncology (preclinical) 85

Table 4.10: Examples of commercial developmental molecular imaging biomarkers in oncology (Phase II, II and III) 86

Table 4.11: Examples of imaging biomarker clinical trials of the Cancer Imaging Program 94

Table 4.12: Examples of molecular imaging biomarkers for the diagnosis and management of Alzheimer's disease 99

Table 4.13: Examples of molecular imaging biomarkers for the diagnosis and management of Parkinson's disease 103

Table 4.14: Examples of commercial developmental molecular imaging biomarkers for cardiovascular disease diagnosis 105

Table 5.15: Companies developing computer aided diagnostic software 119

Table 6.16: Predicted growth rates for outpatient MRI and CT in the US, 2008–2013 128

Table 6.17: The 20 largest academic imaging centers in the US 129

Table 6.18: Examples of companies supplying PET radiopharmaceuticals 136

Table 7.19: FDA fee rates (\$) for the 2010 financial year 151

Table 8.20: Examples of the different types of industry clinical trials involving PET 159

Table 8.21: Examples of the different types of industry clinical trials involving MRI 161

Table 8.22: Effect of HER2 testing on the development of Herceptin 162

Table 8.23: Radiation doses from various types of medical imaging procedures 166