Precision Cancer Medicine

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Role of the Pathologist

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Foreword

Significant progress in the prevention, early detection, and treatment of cancer continues to be made and the death rate from cancer continues to decline. In fact, for each of the last 2 years, we have seen the steepest single-year decline in the cancer death rate on record. Cancer drug therapies have become more precise, surgical treatments less invasive, radiation more targeted, and we are learning additional ways to unleash a patient's immune system against their cancer. At the same time, scientists are unlocking the increasingly complex mechanisms tumor cells use to escape treatment and developing sophisticated diagnostics and drugs to find and treat them. The completion of the human genome sequencing project in 2003 accelerated the ability to determine genetic abnormalities in tumors that can be used to design precision therapeutics. This technological advance has been accompanied by rapid progress in multi-omic technologies, complemented by evolving artificial intelligence and machine learning capabilities. Clearly, there is a bright path forward for further interception and successful treatment of cancer.

As these evolving technologies and therapeutics move forward, the pathologist sits at command central, playing an ever-increasing and critically important role in their application. Of course, the pathologist is always the arbiter of a diagnosis of cancer and an important adjudicator of clinical treatment plans. In the multidisciplinary tumor board, the final word of the pathologist with their real-time review of the tumor histology and its inked margin dictate the next steps in the patient's care. As a practicing surgical, medical, or radiation oncologist, effective relationships with the surgical pathologists are critical for success and are foundational parts of an educational curriculum for trainees.

However, the increasing diagnostic complexity with shifts toward more molecular and morphological-based analytics has created their own set of challenges for the pathologist. In fact, when coupled with the declining pathology workforce, it is becoming increasingly difficult to integrate the latest advances into the routine care of cancer patients. Nonetheless, with challenges, there are always opportunities. For pathologists, the opportunity lies in their position at the tip of the spear of the Fourth Industrial Revolution.[1] This digital revolution started in the middle of the twentieth century and represents the fusion of the physical, digital, and biological worlds with a wide range of new technologies. The speed of breakthroughs already seen in this

1. https://www.weforum.org/agenda/2016/01/the-fourth-industrial-revolution-what-it-means-and-how-to-respond/

revolution is unprecedented and it is both transformational and disruptive. For pathologists, it means moving onward from the light microscope into the myriad of evolving analytic technologies and correlating them with the massive amounts of clinical and outcomes data on cancer patients. For cancer patients, it means better diagnostics, improved precision-based therapeutics, and most importantly, continued improved outcomes.

Finally, as we relish the prospects of what this industrial revolution will bring to the patient with cancer, it is important to remember that we still have widespread disparities in cancer care and cancer outcomes. Sadly, a patient's zip code frequently has a better prediction of their outcome than their genetic code and these disparities are currently widening. However, through existing digital approaches, pathologists can directly solve some of these disparities. In fact, this is already happening. For example, in sub-Saharan Africa, by providing hospitals with tissue processing protocols and slide scanners, central pathological analysis is happening. Pathologists are working together digitally to ensure that accurate diagnoses are rendered to patients in widespread areas. This is one example of how the technological revolution can and will provide positive solutions to cancer disparities, with the pathologist, again, at the center of patient care.

So, there are many reasons to be optimistic about progress in understanding, preventing, diagnosing, and treating cancer. Given the pace of discovery, we likely have little idea of how this will evolve during these transformative times. But one thing appears crystal-clear: the multidisciplinary approach to oncology will have an ever-expanding importance, and the pathologist will remain a critical force behind increasingly successful patient outcomes.

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Preface

Pathologists represent an increasingly scarce healthcare resource worldwide. Optimization of their role is thus critical to sustaining modern cancer diagnosis and patient care. Machine learning/artificial intelligence (ML/AI) is a powerful complementary tool that could aid the pathologists to improve efficiency and provide next-generation interpretation that includes analysis of complex biomarker and genomics data. For this approach to succeed, pathologists must be active in all phases of ML/AI development, from early design and testing through implementation. The alternative is to risk the pathologist being bypassed by non-medical data mining experts, leading to compromised outcomes for the patient due to lack of integration with the complete pathological information. The current increase in automation should lead pathologists to reassess their roles and their true value to the healthcare team, across the entire spectrum of biomarker testing as part of what is essentially a new field of precision oncology.

Part I introduces precision cancer medicine as founded on the principle of providing a highly specific molecularly targeted treatment that, based upon appropriate validated companion tests, is judged to be the most effective therapy for the particular cancer type or subtype affecting the individual patient. This approach has required the development of assays that are capable of identifying as accurately and precisely as possible those actionable molecular target(s) in the cancer cells that are present in the sample or biopsy available for analysis.

In Part II, such assays are described as based on the use of a variety of molecular probes referred to as predictive cancer biomarkers. The specificity and sensitivity of the biomarker-based cancer test, although largely determined by the accuracy and the precision of the analytical method used, are also critically influenced by the quality of the tissue sample and the method used for reading or scoring of the results, both areas of responsibility for the pathologist as described and exemplified in Part III.

Part IV presents the factors that influence the adoption of digital pathology as a complementary aid for patient care purpose. They include the mind-set of the pathologists as well as legal, financial, and technological challenges. The barriers to adoption are gradually breaking down. Digital pathology is gaining momentum, as evidenced by the approval of the first whole slide imaging system for primary diagnosis, recent advances in computational and imaging systems, and the fact that more pathology labs are incorporating digital pathology in their practice. Helpful practical resources, such as

guidelines, validation, and accreditation requirements, will support the implementation of clinical grade digital pathology. Ultimately, however, the pathologist must help to integrate the rapidly moving fields of computer science and medical science. The end goal is to develop a new way of practicing pathology, which we in this book have termed ‘precision pathology’, suited to meet the demands of precision oncology, which itself is continually being reshaped by these very same scientific advances.

Regulatory bodies and expert opinion groups have introduced guidelines to reduce the overall variability of the total test process described in Part II, through recommendations for standardization of the pre-analytical phase involving handling of the tissue material, and the post-analytical phase of interpretation, namely scoring and reporting the results. However, the variability associated with an individual patient sample analysis still must be checked and quality controlled to ensure that the correct result is provided to the cancer physician or the oncologist. As emphasized in Part III, it has increasingly become the role of the pathologist to manage this complex process from bench to bedside, based on their detailed knowledge and unique experience of how predictive cancer biomarker tests are analytically and clinically validated, and exactly what measures are required to implement and run these tests safely and sustainably in routine diagnostic practice.

As we move toward the era of digital and computational pathology, this role continually is being extended, as well as changed, to include management of more stringent quality control of tissue sample handling and new analyses based on more complex biomarker tests as alluded to in Part IV. While many of these responsibilities are grounded in traditional pathology and clinical laboratory practice, the inevitable computer-driven ML/AI interface is largely new to anatomic pathology. Successful adoption will require that the surgical pathologist acquires new skills and new competencies, both through newly developed training programs and by on-the-job interactive experience, as part of an ever evolving learning process.

AI has permeated almost every aspect of our daily lives, from driving across town, to researching for a manuscript, to finding a restaurant, and virtual reality entertainment, in much of which the role of AI is largely subliminal and unnoticed. Surely, it is not beyond the compass of the present generation of pathologists to adopt and shape these powerful ML/AI tools into routine pathology practice, to the benefit of the pathologist, the oncologist, and ultimately the patient: precision medicine begets and demands precision pathology.

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Contents

Part I The Evolution of Pathology and Precision Medicine

1 Introduction: From 'Tissue Diagnosis' to Biomarkers 3
1.1 A Brief History of Pathology: The Progression to Precision Cancer Medicine 3
1.1.1 Cure as a Generic Rationale for Cancer Treatment . . . 3
1.2 The Microscope Invents Pathology and Pathologists 3
1.3 Seeking a Cure for Non-Symptomatic Early Stage Cancer; Cancer Screening 5
1.4 Development of Targeted Therapies 6
References 7

2 The Advent of Biomarker Testing 9
2.1 Biomarkers in Medicine and Cancer 9
2.1.1 Biomarkers in Cancer 10
2.2 Basis of Prediction of Response to Therapy 14
2.3 Role of Pathology and the Pathologist in the Advent of Precision Cancer Medicine 14
2.3.1 New Types of Tests: Companion and Complementary Diagnostics 14
2.3.2 Evolution to Revolution: The Changing Role for Pathology 15
2.4 The Development Pathway for Targeted Therapeutics and Precision Diagnostics 16
References 18

3 The Practical Challenges for Pathology: Multiple Rapidly Evolving Methods 19
3.1 Role in the Development Pathway for Targeted Therapeutics and Precision Diagnostics 19
3.1.1 Pre-Clinical Research 19
3.2 Conversion of IHC from a 'Qualitative' Stain; to a Quantitative Assay 21
3.3 ISH and Multiplex Immunofluorescence Methods for Multiple Biomarkers 23

3.4 FFPE Extraction Based Molecular Methods, PCR, NGS and Proteomics . . . 24
3.5 Going Digital . . . 24
3.6 Virtual Biomarkers—Molecular Morphology in the Digital Dimension . . . 27
3.7 Total Integrative Pathology; the Big Data Problem . . . 29
3.8 Part I as an entry to Parts II, III & IV . . . 29
References . . . 30

Part II Precision Medicine Demands Precision Pathology

4 Evolution of the Total Test Approach to Tissue Based Pathological Analysis . . . 35
4.1 Introduction: The Microscope 'Invented' the Pathologist . . . 35
4.1.1 Re-Invention . . . 35
4.1.2 Morphology Plus . . . 35
4.2 IHC: A Stain 'Repurposed' as an Assay . . . 36
4.3 In-Situ Hybridization . . . 37
4.4 Molecular Extraction Based Methods; Abandoning Morphology? . . . 37
4.5 Emerging Methods in Microscopy and Microimaging . . . 38
4.6 The Total Test: Pre-Analytical, Analytical and Post-Analytical Phases (Table 4.3) . . . 39
References . . . 41

5 Pre-Analytic Phase: Test Selection; Specimen Acquisition and Handling . . . 43
5.1 The Pre-Analytical Phase Defined . . . 43
5.2 Test Selection—'Fit for Purpose' . . . 43
5.3 Digital Pre-Analytic Quality . . . 47
5.4 Turn-Around Time (TAT); Cost; Reimbursement Issues . . . 47
References . . . 48

6 Pre-Analytic Phase: Specimen Type and Acquisition . . . 51
6.1 The Specimen . . . 51
6.2 Excision Biopsy and Surgical Resection . . . 52
6.3 FNA, Core Needle Biopsy . . . 52
6.4 Cytologic Preparations . . . 53
6.5 Liquid Biopsy . . . 53
References . . . 54

7 Pre-Analytical Phase: Biopsy/Tissue Handling and Processing . . . 55
7.1 Pre-Analytical Variables (Table 7.1) . . . 55
7.2 Transport, Warm and Cold Ischemia . . . 55
7.3 Fixation and Paraffin Embedding (FFPE) . . . 57
7.3.1 Total Fixation Time . . . 59
7.3.2 Nature of the Antigen . . . 60
7.3.3 Fixation Time in Relation to Effectiveness of Different Antibodies . . . 60

7.3.4 Antigen Retrieval (in Analytic Phase) 62
7.3.5 Fixation of Tissues Employed for Validation and Controls 62
7.4 Processing 63
7.5 Tissue Sectioning and Storage 64
7.5.1 Sectioning: Thickness 64
7.5.2 Glass Slides 66
7.5.3 Section Storage Time: Cut Slide Stability 66
References 66

8 Analytical Phase: Protocol and Antigen Retrieval 69
8.1 The Analytical Phase Defined 69
8.2 Deparaffinization and Optional Blocking Procedures 72
8.2.1 Blocking Steps 72
8.3 Antigen Retrieval (AR) or Heat Induced Epitope Retrieval (HIER) 73
References 76

9 Analytical Phase: Principles for Immunohistochemistry (IHC) 77
9.1 Reagents and Protocol for Biomarker Labelling; Selection and Validation 77
9.2 Lab Developed Tests (LDTs)—Manual and Automated 77
9.2.1 Manual IHC Stains 79
9.2.2 Automated IHC Stains 79
9.3 Ready to Use IHC Tests (RTUs) 79
9.4 Approved IHC Biomarker Assays (FDA, CE Marked) 80
9.5 Detection Systems and Amplification 80
9.6 Introduction to Fit for Purpose Controls: Required Characteristics 82
9.6.1 The Six Required Characteristics of Controls—Reference Standards 83
9.7 FDA Classification of IHC Tests: Classes I, II and III 86
References 87

10 Analytical Phase: Current Controls; Fit for Purpose Selection and Validation 89
10.1 Guides for Selection of Control Materials 89
10.2 Negative Controls 89
10.2.1 Negative Reagent Controls (See Table 10.2) 89
10.2.2 Negative Tissue Controls: External and Internal 91
10.3 Positive Controls: External and Internal 92
10.3.1 Positive External Tissue Controls 92
10.3.2 Positive Internal Tissue Controls 95
10.4 Tissue Micro-Arrays (TMAs): ‘Sausages’ and Tumor Tissue Banks 96
References 99

11 Analytical Phase: Alternative and New Control Systems 101
11.1 Alternative and New Control Systems 101
11.2 Cell Lines 101

11.3 Faux or Pseudo-Tissues . . . 103
11.4 Protein Spots . . . 105
11.5 Internal Controls and Internal Reference Standards . . . 106
11.6 Quantifiable Internal Reference Standards (QIRS) . . . 109
11.7 Quantitative In Situ Proteomics (QISP) . . . 111
References . . . 112

12 Post-Analytic Phase: Interpretation, Scoring and Reporting of Biopsy Results . . . 115
12.1 Assessment of Controls . . . 115
12.2 Sensitivity and Specificity . . . 115
12.2.1 Positive and Negative Results in Relation to Controls . . . 115
12.2.2 Sensitivity . . . 115
12.2.3 Specificity . . . 116
12.3 Verification and Validation IHC Biomarker Assays . . . 116
12.3.1 Verification . . . 117
12.3.2 Validation . . . 117
12.4 Practical Issues in Validation . . . 118
12.5 Validation of Pre-Analytical and Analytical Phases: LDTs, RTUs and Approved Biomarker Tests . . . 118
12.6 Quality Management Systems (QMS): Quality Assurance (QA), Quality Control (QC) . . . 120
12.6.1 External Quality Assessment and Proficiency Testing . . . 121
References . . . 123

13 Description and Interpretation of Results; The Pathology Report . . . 125
13.1 Content and Organization of Report . . . 125
13.1.1 Descriptive . . . 125
13.1.2 Integrated and Standardized Reporting . . . 126
13.2 Scoring; Including Validation of Scoring Method . . . 126
13.3 Scoring Systems . . . 129
13.4 Percentage Based Scores . . . 129
13.4.1 Conversion to Positive and Negative Results . . . 129
13.4.2 Percentage Combined with Intensity and/or Pattern . . . 130
13.4.3 Concordance Training . . . 130
13.4.4 Consensus or Ring Studies . . . 130
13.5 Addition of Immune Cell Assessment . . . 131
13.5.1 Immune Scoring; Immunoscore . . . 131
13.5.2 Composite or Proportion Scores . . . 131
13.5.3 Field of View (FOV) Selection Errors . . . 131
13.6 Phenotypic Cell Identification and Scoring: Multiplex Methods . . . 132
13.7 Digital Computerized Scoring Algorithms . . . 132
References . . . 134

14 Immunofluorescence, In Situ Hybridization and Alternative Forms of 'Labeled' Microscopy 137
14.1 Labeled Microscopy Methods 137
14.2 Immunofluorescence—IF 137
14.3 In Situ Hybridization—ISH 138
14.4 RNA Scope 141
14.5 Advanced Multiplex Microscopy and Other Emerging Methods 142
14.5.1 Brightfield (IHC) Versus Immunofluorescence (IF) Methods 142
14.5.2 Multiplex Digital IF 143
14.6 MIBI Microscopy (Multiplex Ion Beam Imaging) 148
14.7 Raman Microscopy (Vibrational) Spectroscopy (RMS) 148
14.8 Part II—Summary 151
References 151

Part III Role of the Pathologist in Predictive Biomarker Analysis

15 Implementation of Precision Cancer Diagnostic Test 155
15.1 Introduction to Role of the Pathologist in Predictive Biomarker Analysis 155
15.2 Implementation of Predictive Biomarker Tests 157
15.3 Analytical Validation 157
15.3.1 Repeatability 159
15.3.2 Intermediate Precision 159
15.3.3 Role of the Pathologist in Repeatability and Intermediate Studies 159
15.3.4 Reproducibility 160
15.3.5 Total Test Reproducibility 160
15.3.6 Role of the Pathologist in Assay Reproducibility Studies 160
15.4 Clinical Validation 161
15.4.1 The Role of the Pathologist 162
15.5 Clinical Utility 163
15.5.1 The Role of the Pathologist 163
15.6 Summary & Future Needs & Trends 165
References 166

16 Role of Pathologist in Precision Cancer Diagnosis 169
16.1 Introduction 169
16.2 Regulatory Body and Expert Opinion Based Recommendations 170
16.3 Role of Pathologist in Assurance of Good Diagnostic Practice 171
16.4 Internal Quality Assurance of Pre-Analysis Phase 174
16.4.1 Potential Errors Due to Inadequate Tissue Preservation 174
16.4.2 Adequacy and Representativeness of Biopsy Material 174

16.5 Internal Quality Assurance of Analysis Phase 175
16.5.1 Pre-Analytic Phase Exclusion Factors 175
16.5.2 Analytic Phase Exclusion Factors 175
16.5.3 Evaluation of the Quality of Biopsy Material 177
16.5.4 Evaluation of Distribution and Quantity of Tumour Tissue 177
16.5.5 Assessment of Quality of Assay Performance 177
16.5.6 Selection and Use of Control 178
16.6 Quality Assurance of Post-Analytic Phase 178
16.6.1 Post Analysis Factors Influencing Quality of Biomarker Assessment 178
16.6.2 Indication Specific Interpretation, Scoring and Reporting 178
16.6.3 Assessment of Appropriateness and Completeness of Biomarker Analysis 179
16.6.4 Evaluation of Accuracy of the Results 179
16.7 Summary and Future Needs & Trends 180
References 180

17 Role of Pathologist in Precision Molecular and Digital Image Analyses 183
17.1 Introduction 183
17.2 Role of Pathologist in Morpho-Molecular Diagnosis of Cancer 184
17.3 Role of Pathologist in Molecular Analysis of Cancer 186
17.4 Role of Pathologist in Guidance of Cancer Molecular Profiling 186
17.5 Role of Pathologist in Analysis of Tumour Heterogeneity 189
17.6 Role of Pathologist in Analysis of Tumour Micro-Environment (TME) 190
17.7 Future Role of Pathologist in Emerging Morpho-Molecular Cancer Diagnostics 192
References 193

Part IV Digital and Computational Pathology and Their Role in Precision Oncology

18 Introduction to Digital and Computational Pathology 199
References 203

19 AI in the Pre-Analytical Phase 205
19.1 The Workflow Design 205
19.2 Sample and Quality Management 206
19.3 Quality Control and Validation 207
19.4 CIS, LIS, DIS and PACS 208
19.5 Workflow Integration, Connectivity and Interoperability 208
References 210

20 AI in the Analytical Phase . . . 211
20.1 Overcoming Variabilities . . . 211
20.2 Telepathology . . . 211
20.3 Standardization, Harmonization and Concordance . . . 212
20.4 Scanning and Whole Slide Imaging . . . 212
20.5 Image Analysis . . . 213
20.6 Advanced Microscopy . . . 214
References . . . 215

21 AI in the Post-Analytical Phase . . . 217
21.1 Dealing with Complexity . . . 217
21.2 Artificial Intelligence, Machine Learning and Topology . . . 217
21.3 Computational Pathology . . . 219
21.4 The Science of Data or Data Science . . . 219
21.5 Algebraic Pathology . . . 221
21.6 Encoded Pathology . . . 221
21.7 Disease Modelling and Simulation . . . 222
References . . . 223

22 AI in the Decision Phase . . . 225
22.1 Examples of Clinical Utility . . . 225
22.2 Prognosis of Cancer . . . 225
22.3 Predicting Treatment Outcomes . . . 225
22.4 Clinical Decision Support Through Applications . . . 226
22.4.1 Colorectal Cancer . . . 226
22.4.2 Lung Cancer . . . 227
22.4.3 Melanocytic Lesions . . . 227
22.4.4 Lymphoid Aggregates . . . 227
22.4.5 Bladder Cancer . . . 228
22.4.6 Renal Biopsies . . . 228
22.4.7 Breast Cancer . . . 228
22.4.8 Prostate Cancer . . . 229
22.4.9 Thyroid Cancer . . . 229
22.4.10 Cytology . . . 230
22.4.11 Biobanking . . . 230
22.5 Opportunity for Discovery of Novel Biomarker . . . 231
References . . . 231

Index . . . 233