Handbook of Practical Immunohistochemistry

Fan Lin • Jeffrey W. Prichard • Haiyan Liu
Myra L. Wilkerson • Yi Ding
Editors

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Frequently Asked Questions

Fourth Edition

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Editors
Fan Lin, MD, PhD
Department of Laboratory Medicine
Geisinger Health System
Danville, PA, USA

Haiyan Liu, MD
Department of Laboratory Medicine
Geisinger Health System
Danville, PA, USA

Yi Ding, MD, PhD
Department of Laboratory Medicine
Geisinger Health System
Danville, PA, USA

Jeffrey W. Prichard, DO
Department of Laboratory Medicine
Geisinger Health System
Danville, PA, USA

Myra L. Wilkerson, MD
Department of Laboratory Medicine
Geisinger Health System
Danville, PA, USA

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Preface to the Fourth Edition

As in the previous editions, the fourth edition of *Handbook of Practical Immunohistochemistry: Frequently Asked Questions* is written in a question-and-answer (Q&A) format and intended to be a practical, user-friendly, quick reference for information related to using the most up-to-date immunohistochemistry, in situ hybridization, and molecular oncologic pathology in clinical diagnosis. The new edition demonstrates a significant revision and improvement over the third edition in many ways summarized as follows:

1. *Two new chapters*: This is the most important addition to the fourth edition. Two new chapters on molecular oncologic pathology have been added: (1) molecular oncologic pathology of solid and soft tissue tumors; and (2) molecular oncologic pathology of hematologic tumors. Molecular pathology has gained its popularity and has been fully integrated into daily practice in anatomic pathology. In addition to identifying targeted specific mutations/molecular alterations for therapeutic purposes, molecular testing is playing an important role in evaluating solid tumors, soft tissue tumors, and hematologic tumors. For example, a CK7-positive carcinoma lacking site-specific markers undergoes molecular testing and demonstrates *KRAS* mutations. Given that *KRAS* mutations are more commonly detected in pancreatic and lung tumors, if *KRAS* G12R mutation is detected, this could be used to favor a pancreatic origin in the appropriate clinical setting; in contrast, if *KRAS* G12C mutation is detected, a lung primary is favored since *KRAS* G12C mutations are more commonly seen in lung adenocarcinomas. This ability to use molecular testing to definitively determine or favor an origin is becoming increasingly common as we continuously improve our understanding of the molecular signature of different tumors.
2. *Extensive additions and changes*: Significant additions and revisions have made to many chapters. For example, in Chap. 8, many more recently described IHC markers, such as TRPS1, SOX17, POU2F3, SS18-SSX, SSX, NR4A3, CAP1, etc., have been included and discussed. Many IHC panels have been revised with more sensitive and specific markers, and many new references have been added.
3. *More questions and answers*: Over 100 new questions and answers have been added to the fourth edition. All chapters have been updated to include relevant new questions, new markers, more refined IHC panels, representative pictures, and current references.
4. *More refined working antibody panels*: When you examine each individual table, you will notice that some of the antibodies in the table are highlighted. The highlighted set of antibodies is the suggested and refined panel for an initial workup. Brief notes are provided for many tables in order to reiterate the most important diagnostic applications and pitfalls that one may encounter.
5. *More new diagnostic and predictive biomarkers*: Many recently described antibodies in clinical IHC laboratories have been added. These include many recently described diagnostic markers such as TRPS1, SOX17, POU2F3, SS18-SSX, SSX, DDIT3, NR4A3, CPA1, claudin 18, MTAP, merlin, SOX6, and NKX6-1.
6. *More high-quality color pictures from Geisinger Medical Laboratories (GML) IHC slides*: An extensive set of high-quality color pictures and diagnostic algorithms, if available, is included in each chapter to illustrate some of the key antibodies, including many recently

discovered and substantiated antibodies used in that chapter. There are over 800 color pictures taken from GML IHC, RNA ISH, and FISH slides using the recommended staining protocols contained in the updated Appendix of this book.

7. *More GML data*: In many tables you will see comparisons of data from GML to data from the literature. This is a unique feature of this book. The reproducibility of antibodies reported in the literature is sometimes in question; to improve the reproducibility, we have undertaken the daunting task of testing the antibodies listed in the appendix using more than 10,000 TMA slides and 2000 routine slides. These TMA sections contain thousands of tumors from various organs and normal tissues in the GML archives. If your lab follows the protocols in the updated Appendix for automated staining procedures, you should obtain results like ours.
8. *Updated appendix*: The updated Appendix contains detailed antibody information for automated immunostaining procedures for over 250 antibodies available at Geisinger IHC Laboratory.
9. *IHC on normal tissues*: Immunophenotypes of many normal tissues, which receive little or no attention in other surgical pathology and IHC books, have been included in many chapters, such as normal breast, lung, pancreas, ampulla, colon, stomach, small intestine, kidney, etc.
10. *More current references*: A large number of current references have been included in each new and updated chapter.
11. *Data interpretation*: To standardize our manual scoring system, unless otherwise specified, the following criteria are applied throughout this book:
    - − = usually less than 5% of cases are stained
    - + = usually greater than 70% of cases are stained
    - + or − = usually more than 50% but less than 70% of cases are stained
    - − or + = usually less than 50% of cases are stained
    - V = variable, or sometimes positive; data are somewhat inconsistent
    - ND = no data available
12. *More expert contributions*: Last but not least, many chapters also include contributions from an expert in his or her field.

After publication of the previous editions, we received overwhelmingly positive feedback and valuable suggestions and comments from readers, and we would like to take this opportunity to express our very sincere thanks to all of you. As always, the editors ask for your understanding of any potential errors in this new edition and also invite you to submit your feedback, suggestions, and comments to us (flin1@geisinger.edu; jwprichard@geisinger.edu; hliu1@geisinger.edu; mwilkerson@geisinger.edu; yding1@geisinger.edu). With continued support from readers like you, we are confident that each future edition will be even more complete and informative than the previous one.

Danville, PA, USA — Fan Lin, MD, PhD
Danville, PA, USA — Jeffrey W. Prichard, DO
Danville, PA, USA — Haiyan Liu, MD
Danville, PA, USA — Myra L. Wilkerson, MD
Danville, PA, USA — Yi Ding, MD, PhD

Acknowledgments

It has been 14 years since the publication of the first edition. Producing the fourth edition of this IHC Handbook was as challenging for our department as was publishing the previous editions, and we wish to acknowledge the assistance and tremendous support we received from our leadership team and staff. Diana Kremitske, Vice President, Operations, Diagnostic Medicine Institute, supported and encouraged this project from conception through completion. Sandy Mullay, Operations Director of Anatomic Pathology, always ensured we had the technical, secretarial, and clerical support needed for all phases of the project. Amie Brown served as our project coordinator, scheduling many meetings, working closely with Springer, keeping us organized, and moving the project forward. Melissa Erb and the pathology residents (Drs. Liping Li, Haluk Kavus, and Sahrish Shah) collected thousands of new references from the six most popular pathology journals from 2020 to today and organized them into subspecialty folders. As for the last three editions, Kathy Fenstermacher was invaluable in editing, formatting, and polishing book chapters, creating an EndNote library for thousands of references, as well as producing many diagrams. Without Kathy's and Amie's tireless efforts, it would not have been possible to meet the fourth edition submission deadline. Christy Attinger worked closely with Amie to ensure that authors had some protected time to work on their chapters. John Shaw constructed many TMA blocks for testing and studying many new antibodies. Angela Bitting and Jianhui Shi are responsible for bringing you the hundreds of optimized IHC protocols available in Appendix of this book. Tina Brosious, Laurie Kneller-Walter, Deanna Ward, Beth Reigle, Kris Bricker, and Kathryn Powell, immunohistochemical technologists, performed IHC stains on numerous tissue microarray sections and routine slides. Stacey Fague, System Manager for Anatomic Pathology, helped with scheduling and coordination of technical staff. A special thanks to Dr. Rob Monroe (Chief Scientific Officer for Oncology, Danaher Diagnostics) for his contribution to Chap. 5. Finally, we are in debt to our families and close friends for their understanding that we have again buried ourselves in this exciting project for such an extended period. As always, we wholeheartedly thank you for your incredible support.

Fan Lin, MD, PhD
Jeffrey W. Prichard, DO
Haiyan Liu, MD
Myra L. Wilkerson, MD
Yi Ding, MD, PhD

Contents

Contributors

Tina K. Agander, MD, PhD University Hospital of Copenhagen, Rigshospitalet, Copenhagen, Denmark

Ali Amin, MD Brown University Health, The Miriam Hospital, Providence, RI, USA

Evans C. Bailey, MD, PhD, FAAD, FACMS Naaman Clinic Surgical Dermatology, Birmingham, AL, USA

Angela K. Bitting, HT (ASCP), QIHC Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Andrew Campbell, PhD Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Zongxian Cao, MD, PhD Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Wells Chandler, MD Dermatopathology Section, Department of Laboratory Medicine Geisinger Medical Center, Danville, PA, USA

Guoli Chen, MD, PhD Department of Pathology, Penn State Health Hershey Medical Center, Hershey, PA, USA

Zongming E. Chen, MD, PhD Mayo Clinic, Rochester, MN, USA

Liang Cheng, MD Legorreta Cancer Center at Brown University, Providence, RI, USA

Kristi Cressman, HT, IQHCcm Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Hongbing Deng, MD, PhD Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Mary Dhesi, MD Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Yi Ding, MD, PhD Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Dirk M. Elston, MD Medical University of South Carolina, Charleston, SC, USA

Tammie Ferringer, MD Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Renee Frank, MD Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Jerad M. Gardner, MD Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Lawrence E. Gibson, MD Department of Dermatology, Mayo Clinic College of Medicine, Rochester, MN, USA

Michelle Grant, DO Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Sophia Greely, NA Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Stephen Hewitt, PhD Laboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

Julie W. Hirschhorn, PhD Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Zachary S. Hoffer, MD, PhD Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Jialing Huang, MD, PhD Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Justin R. Jefferson, BS, MB(ASCP)cm, HTLcm Novodiax, Inc., Hayward, CA, USA

Jacqueline M. Junkins-Hopkins, MD Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Haluk Kavus, MD Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Syed AJ Kazmi, MD Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Jeffrey Kleinberger, MD, PhD Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Heinz Kutzner, MD Dermatopathologische Gemeinschaftspraxis, Friedrichshafen, Germany

Jordan Laser, MD Bio-Techne, Austin, TX, USA

Hongjie Li, MD, PhD Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Jianhong Li, MD, PhD Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Jinhong Li, MD, PhD Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Liping Li, MD, PhD Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Fan Lin, MD, PhD Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Haiyan Liu, MD Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Mark Mentrikoski, MD Department of Pathology and Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Sara E. Monaco, MD Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Michelle Pramick, MD Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Jeffrey W. Prichard, DO Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

William Quinones, MD Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Sahrish Shah, MD Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Jianhui Shi, MD, PhD Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Dana Snyder, BS, CT (ASCP)cm Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Farnaz C. Tahmasebi, MD Department of Pathology and Laboratory Medicine, Geisinger Health System, Danville, PA, USA

William B. Tyler, MD Dermatopathology Section, Department of Laboratory Medicine, Geisinger Medical Center, Danville, PA, USA

Hanlin L. Wang, MD, PhD Department of Pathology and Lab Medicine, University of California Los Angeles, Los Angeles, CA, USA

Sara Waqar, MD Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Myra L. Wilkerson, MD Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Ximing J. Yang, MD, PhD Northwestern University, Feinberg School of Medicine, Northwestern Memorial Hospital, Chicago, IL, USA

Hong Yin, MD Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Michele K. Zelonis, CT (ASCP) Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Kai Zhang, MD Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Linsheng Zhang, MD, PhD Emory University School of Medicine, Emory Healthcare Medical Laboratories, Emory University Hospital, Atlanta, GA, USA

Xiaohong (Mary) Zhang, MD, PhD Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA

Song Q. Zhao, MD, PhD, MPH Novodiax, Inc., Hayward, CA, USA

Shaobo Zhu, MD Department of Laboratory Medicine, Geisinger Health System, Danville, PA, USA