Sixth Edition

Basic Skills in INTERPRETING LABORATORY DATA

MARY LEE

ashp publications

Sixth Edition

Basic Skills in INTERPRETING LABORATORY DATA

Mary Lee, PharmD, BCPS, FCCP
Vice President
Chief Academic Officer
Pharmacy and Optometry Education
Midwestern University
Professor, Pharmacy Practice
Midwestern University Chicago College of Pharmacy
Downers Grove, Illinois

ashp® publications

Any correspondence regarding this publication should be sent to the publisher, American Society of Health-System Pharmacists, 4500 East-West Highway, Suite 900, Bethesda, MD 20814, attention: Special Publishing.

The information presented herein reflects the opinions of the contributors and advisors. It should not be interpreted as an official policy of ASHP or as an endorsement of any product.

Because of ongoing research and improvements in technology, the information and its applications contained in this text are constantly evolving and are subject to the professional judgment and interpretation of the practitioner due to the uniqueness of a clinical situation. The editors and ASHP have made reasonable efforts to ensure the accuracy and appropriateness of the information presented in this document. However, any user of this information is advised that the editors and ASHP are not responsible for the continued currency of the information, for any errors or omissions, and/or for any consequences arising from the use of the information in the document in any and all practice settings. Any reader of this document is cautioned that ASHP makes no representation, guarantee, or warranty, express or implied, as to the accuracy and appropriateness of the information contained in this document and specifically disclaims any liability to any party for the accuracy and/or completeness of the material or for any damages arising out of the use or non-use of any of the information contained in this document.

Editorial Project Manager, Books and eLearning Courses: Ruth Bloom
Editorial Project Manager, Publications Production Center: Kristin Eckles
Cover and Page Design: David Wade

Library of Congress Cataloging-in-Publication Data

Names: Lee, Mary (Mary Wun-Len), editor. | American Society of Health-System Pharmacists, issuing body.
Title: Basic skills in interpreting laboratory data / [edited by] Mary Lee.
Description: Sixth edition. | Bethesda, MD: American Society of Health-System Pharmacists, [2017] | Includes bibliographical references and index.
Identifiers: LCCN 2016016112 | ISBN 9781585285488
Subjects: | MESH: Clinical Laboratory Techniques | Reference Values | Clinical Laboratory Services
Classification: LCC RB37 | NLM QY 25 | DDC 616.07/5--dc23 LC record available at https://lccn.loc.gov/2016016112

ISBN: 978-1-58528-548-8

10 9 8 7 6 5 4 3 2 1

DEDICATION

This book is dedicated to all of the chapter authors and reviewers, whose commitment to the education of future health professional students is evident in all that they do.

Mary Lee

CONTENTS

ACKNOWLEDGMENTS

I express my sincere gratitude to the publishing staff at ASHP in the preparation of this book: Ruth Bloom, who assisted me 24-7 and answered my many e-mails; Amberly Hyden, who maintained all of the contract paperwork; Kristin Eckles, who has the best eyes for details; and Jack Bruggeman, who has consistently supported this project for more than a decade.

Mary Lee

PREFACE

The last four editions of *Basic Skills in Interpreting Laboratory Data* have been made possible by the dedicated chapter authors, reviewers, and the publishing staff at the American Society of Health-System Pharmacists. It has been my honor to serve as the editor and to work with this team.

For this sixth edition, approximately 90% of the lead authors have served in this capacity for the earlier editions with some exceptions. Paul O. Gubbins, PharmD, and Heather Lyons-Burney, PharmD, joined as the lead authors of a new chapter on Point-of-Care Testing, and Nicholas M. Moore, MS, MLS (ASCP), updated the chapter on Introduction to Common Laboratory Assays and Technology. All of the lead authors are established clinicians and/or experienced faculty at colleges of pharmacy or medicine, which enhance the quality of the chapter content.

A whole new group of reviewers has joined this project, and many reviewers are board-certified or established experts. Their specialty knowledge and scrutiny of the chapter content have helped to ensure that each chapter is up-to-date and content is relevant to clinical practice. As you use this book, you will find that the sixth edition includes updated chapter content with references, and almost all of the chapters have at least one new Minicase and Learning Point. In addition, the Abbreviations in the front of the book and the Glossary in the back have been expanded for reader convenience.

Significant and notable new chapter content:

1. Hematology: Blood Coagulation Tests includes expanded sections on laboratory tests to monitor direct thrombin inhibitors, direct oral anticoagulants, and low molecular weight heparin.
2. Hematology: Red and White Blood Cell Tests includes a discussion of cell types, associated cluster of differentiation epitopes or targets, and FDA-approved targeted therapies.
3. Infectious Diseases includes an expanded section on molecular diagnosis of specific viral nucleic acids and 1,3-β-glucan detection of fungi.
4. Liver and Gastroenterology Tests includes a new section on laboratory tests to diagnose and monitor hemochromatosis.
5. Interpretation of Serum Drug Concentrations includes information on new medications that have become commercially available since the last edition.
6. Men's Health includes an expanded section on PSA testing for screening, staging, and monitoring treatment of prostate cancer.

Suggestions for using this book efficiently:

- For a general overview of the laboratory tests for various organ systems or types of diseases, use the table of contents to identify the most appropriate section or chapter(s). The chapters are grouped into three major sections: Basic Concepts and Test Interpretations, System Disorders and Diagnostic Tests, and Tests for Special Populations. By reading the section or a chapter from start to finish, you get a detailed summary of the laboratory tests used to evaluate that organ system or disease, why the test is used, what a normal value range is for the test, and how to interpret an abnormal laboratory test result. Minicases guide the reader through common clinical scenarios about ordering appropriate laboratory tests, interpreting results, managing patients, and addressing spurious laboratory tests. Learning points conclude each chapter and highlight key concepts about the laboratory tests. Using the book in this way will be helpful, especially when used as a companion to a disease state management course, a pharmacotherapeutics course, or a course that prepares students for full-time clinical rotations.
- For information on a specific laboratory test, use the alphabetical index to locate the test, and then go to the page(s) to access the following information: the purpose of the test; how the test result relates to the pathophysiology of a disease or the physiologic function of a cell or organ;

the normal range for the test; causes for an abnormal test result; and causes of false-positive or false-negative results. This approach will be most useful in the clinical management of a patient.

- Quickview charts are provided for some of the most common laboratory tests. These charts are standardized template presentations of information that allow readers to quickly learn about a specific laboratory test (e.g., what the test is used for, what a normal result is, and causes of an abnormal result). This approach also will be most useful in the clinical management of a patient, but the Quickview content should be supplemented with the in-depth information in the chapters about a particular laboratory test. Although this book does not provide Quickview charts for all of the laboratory tests discussed, readers can refer to other clinical laboratory test handbooks, such as ASHP's *Interpreting Laboratory Data: A Point-of-Care Guide*.

The authors, reviewers, and I hope that *Basic Skills in Interpreting Laboratory Data* is useful to your practice.

Mary Lee
May 2017

CONTRIBUTORS

EDITOR AND CONTRIBUTOR

Mary Lee, PharmD, BCPS, FCCP
Vice President
Chief Academic Officer
Pharmacy and Optometry Education
Midwestern University
Professor, Pharmacy Practice
Midwestern University Chicago College of Pharmacy
Downers Grove, Illinois

CONTRIBUTORS

Brian Altman, MD
Western Mass GI Associates
Springfield, Massachusetts

Jason M. Altman, DO
Department of Anesthesiology
University of Connecticut Health Center
Farmington, Connecticut

Candi C. Bachour, PharmD
Department of Clinical Pharmacy
University of Tennessee Health Science Center
Memphis, Tennessee

Jeffrey F. Barletta, PharmD, FCCM
Professor and Vice-Chair
Department of Pharmacy Practice
Midwestern University College of Pharmacy—Glendale
Glendale, Arizona

Amber L. Beitelshees, PharmD, MPH, FAHA
Assistant Professor
Division of Endocrinology, Diabetes, and Nutrition
University of Maryland—Baltimore
Baltimore, Maryland

Jill S. Borchert, PharmD, BCACP, BCPS, FCCP
Professor and Vice-Chair, Pharmacy Practice
Director, PGY2 Ambulatory Care Residency Program
Midwestern University Chicago College of Pharmacy
Downers Grove, Illinois

Jaclyn A. Boyle, PharmD, MS, MBA, BCPS
Assistant Professor for Community Pharmacy Innovation
Pharmacy Practice Department
Northeast Ohio Medical University
Rootstown, Ohio

Candace S. Brown, PharmD, MSN
Professor of Clinical Pharmacy and Psychiatry
University of Tennessee Health Science Center
Memphis, Tennessee

Susan P. Bruce, PharmD, BCPS
Associate Dean of Pharmacy Education and Interprofessional Studies
College of Pharmacy
Chair and Professor
Pharmacy Practice
Northeast Ohio Medical University
Rootstown, Ohio

Rodrigo M. Burgos, PharmD
Clinical Assistant Professor
College of Pharmacy
University of Illinois at Chicago
Chicago, Illinois

Lingtak-Neander Chan, PharmD, BCNSP, FACN
Professor and Vice Chair
Department of Pharmacy
Interdisciplinary Faculty in Nutritional Sciences
School of Pharmacy & Graduate Program in Nutritional Sciences
University of Washington
Seattle, Washington

Rosane Charlab, PhD
Genomics Group, Office of Clinical Pharmacology
Office of Translational Sciences
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Silver Spring, Maryland

Peter A. Chyka, PharmD
Professor and Executive Associate Dean
College of Pharmacy, Knoxville Campus
The University of Tennessee Health Science Center
Knoxville, Tennessee

Samir Y. Dahdal, MD, FACC
Noninvasive Cardiologist
Tucson Heart Group
Tucson Medical Center
Tucson, Arizona

Wafa Y. Dahdal, PharmD, BCPS
Director of International Programs
Associate Director of Professional Development
American College of Clinical Pharmacy
Lenexa, Kansas

Lea E. Dela Peña, PharmD, BCPS
Associate Professor, Pharmacy Practice
Midwestern University Chicago College of Pharmacy
Downers Grove, Illinois

Sharon M. Erdman, PharmD
Clinical Professor of Pharmacy Practice
Purdue University College of Pharmacy
Infectious Diseases Clinical Pharmacist
Eskenazi Health
Indianapolis, Indiana

Paul Farkas, MD, AGAF, FACP
Chief of Gastroenterology
Mercy Hospital
Assistant Clinical Professor of Medicine
Tufts University School of Medicine
Springfield, Massachusetts

Riane J. Ghamrawi, PharmD, BCPS
Clinical Pharmacist Specialist
Adult Antimicrobial Stewardship
University Hospitals Cleveland Medical Center
Cleveland, Ohio

Paul O. Gubbins, PharmD
Associate Dean
Vice Chair and Professor
Division of Pharmacy Practice and Administration
UMKC School of Pharmacy at MSU
Springfield, Missouri

Paul R. Hutson, PharmD, BCOP
Professor, Pharmacy Practice
University of Wisconsin School of Pharmacy
Madison, Wisconsin

Jamie Jensen, PharmD
Western Mass GI Associates
Springfield, Massachusetts

Min J. Joo, MD, MPH, FCCP
Associate Professor of Medicine
Department of Medicine
University of Illinois at Chicago
Chicago, Illinois

Kathy E. Komperda, PharmD, BCPS
Associate Professor, Pharmacy Practice
Midwestern University Chicago College of Pharmacy
Downers Grove, Illinois

Donna M. Kraus, PharmD, FAPhA, FCCP, FPPAG
Associate Professor of Pharmacy Practice
Departments of Pharmacy Practice and Pediatrics
Colleges of Pharmacy and Medicine
University of Illinois at Chicago
Chicago, Illinois

Heather Lyons-Burney, PharmD
Clinical Assistant Professor
UMKC School of Pharmacy at MSU
Springfield, Missouri

Janis J. MacKichan, PharmD, FAPhA
Professor, Department of Pharmacy Practice
Northeast Ohio Medical University
Rootstown, Ohio

Patrick J. Medina, PharmD, BCOP
Associate Professor of Pharmacy
University of Oklahoma College of Pharmacy
Oklahoma City, Oklahoma

Nicholas M. Moore, MS, MLS (ASCP)^{CM}
Assistant Director
Division of Clinical Microbiology
Assistant Professor
Department of Medical Laboratory Science
Rush University Medical Center
Chicago, Illinois

Keith A. Rodvold, PharmD, FCCP, FIDSA
Professor of Pharmacy Practice and Medicine
Colleges of Pharmacy and Medicine
University of Illinois at Chicago
Chicago, Illinois

Joanna Sampson, MD
Western Mass GI Associates
Springfield, Massachusetts

Sarah A. Schmidt, PharmD, BCPS, BCOP
Clinical Assistant Professor—Hematology/Oncology
University of Oklahoma College of Pharmacy
Oklahoma City, Oklahoma

Terry L. Schwinghammer, PharmD, BCPS, FASHP, FAPhA, FCCP
Professor and Chair
Department of Clinical Pharmacy
School of Pharmacy
West Virginia University
Morgantown, West Virginia

Roohollah Sharifi, MD, FACS
Section Chief of Urology
Jesse Brown Veterans Administration Hospital
Professor of Urology and Surgery
University of Illinois College of Medicine
Chicago, Illinois

Barry Slitzky, MD
Western Mass GI Associates
Springfield, Massachusetts

Karen J. Tietze, PharmD
Professor of Clinical Pharmacy
Department of Pharmacy Practice and Pharmacy Administration
University of the Sciences
Philadelphia College of Pharmacy
Philadelphia, Pennsylvania

Dominick P. Trombetta, PharmD, BCPS, CGP, FASCP
Associate Professor, Pharmacy Practice
Wilkes University
Wilkes-Barre, Pennsylvania

Eva M. Vivian, PharmD, MS
Professor, Pharmacy Practice
University of Wisconsin—Madison School of Pharmacy
Madison, Wisconsin

Lori A. Wilken, PharmD, BCACP
Clinical Assistant Professor, Pharmacy Practice
University of Illinois at Chicago College of Pharmacy
Chicago, Illinois

REVIEWERS

Nabila Ahmed-Sarwar, PharmD, BCPS, CDE
Wegmans School of Pharmacy
St. John Fisher College
Clinical Pharmacy Specialist
Department of Family Medicine
University of Rochester School of Medicine and Dentistry
Rochester, New York

Debra J. Barnette, PharmD, BCACP, BCPS
Assistant Professor of Pharmacy Practice
The Ohio State University
Columbus, Ohio

Scott J. Bergman, PharmD, BCPS
Antimicrobial Stewardship Coordinator
Nebraska Medicine
Clinical Associate Professor
University of Nebraska Medical Center
Omaha, Nebraska

Kristen Bova Campbell, PharmD, BCPS-AQ Cardiology, CPP
Clinical Pharmacist and Senior Research Associate, Electrophysiology
Director, PGY2 Cardiology Residency
Duke University Hospital
Durham, North Carolina

Eric G. Boyce, PharmD
Associate Dean for Academic Affairs
Professor of Pharmacy Practice
Thomas J. Long School of Pharmacy and Health Sciences
University of the Pacific
Stockton, California

Larry W. Buie, PharmD, BCOP, FASHP
Clinical Specialist in Leukemia
Memorial Sloan Kettering Cancer Center
New York, New York

Shareen El-Ibiary, PharmD, BCPS, FCCP
Professor of Pharmacy Practice
Department of Pharmacy Practice
Midwestern University College of Pharmacy—Glendale
Glendale, Arizona

Jacob Gettig, PharmD, MPH, BCPS, CHCP
Assistant Dean for Postgraduate Education
Professor of Pharmacy Practice
Midwestern University Chicago College of Pharmacy
Downers Grove, Illinois

Aaron P. Hartmann, PharmD, BCPS
Assistant Professor of Pharmacy Practice
St. Louis College of Pharmacy
St. Louis, Missouri

Julie M. Koehler, PharmD, FCCP
Associate Dean for Clinical Education and External Affiliations
Professor of Pharmacy Practice
Butler University College of Pharmacy and Health Sciences
Indianapolis, Indiana

Larry J. Kricka, DPhil
Professor of Pathology and Laboratory Medicine
The Hospital of the University of Pennsylvania
Director, General Chemistry
Director, Critical Care Laboratory
Interim Director, Endocrine Laboratory
University of Pennsylvania Perelman School of Medicine
Philadelphia, Pennsylvania

Taimour Langaee, MSPH, PhD
Department of Pharmacotherapy and Translational Research
Center for Pharmacogenomics
University of Florida, College of Pharmacy
Gainesville, Florida

Jacqueline L. Olin, PharmD, MS, BCPS, CDE, FASHP, FCCP
Professor of Pharmacy
Wingate University School of Pharmacy
Wingate, North Carolina

Carrie S. Oliphant, PharmD, FCCP, BCPS-AQ Cardiology, AACC
Cardiology/Anticoagulation Clinical Pharmacy Specialist
Methodist University Hospital
Associate Professor
University of Tennessee College of Pharmacy
Memphis, Tennessee

Frank P. Paloucek, PharmD, DABAT, FASHP
Clinical Professor, Pharmacy Practice
College of Pharmacy
University of Illinois at Chicago
Chicago, Illinois

Theresa Prosser, Pharm D, FCCP, BCPS, AE-C
Professor of Pharmacy Practice
Department of Pharmacy Practice
St. Louis College of Pharmacy
St. Louis, Missouri

Erin Raney, PharmD, BC-ADM, BCPS
Professor of Pharmacy Practice
Midwestern University College of Pharmacy—Glendale
Glendale, Arizona

Claire Saadeh, PharmD, BCOP
Professor, Pharmacy Practice
Oncology, Pain Management, Palliative Care
Ferris State University
Department of Pharmacy
Sparrow Health System
Lansing, Michigan

Justin M. Schmidt, PharmD, BC-ADM, BCPS
Associate Professor, Pharmacy Practice
Midwestern University Chicago College of Pharmacy
Downers Grove, Illinois

Carrie A. Sincak, PharmD, BCPS, FASHP
Assistant Dean for Clinical Affairs and Professor
Midwestern University Chicago College of Pharmacy
Downers Grove, Illinois

Curtis L. Smith, PharmD, BCPS
Professor
Ferris State University College of Pharmacy
Sparrow Health System
Lansing, Michigan

James C. Thigpen, PharmD, BCPS
Associate Professor
Department of Pharmacy Practice
Bill Gatton College of Pharmacy
East Tennessee State University
Johnson City, Tennessee

Lori Wazny, PharmD, EPPh
Extended Practice Pharmacist—Manitoba Renal Program
Department of Pharmaceutical Services
Health Sciences Centre
Winnipeg, Manitoba
Canada

ABBREVIATIONS

μm	micrometer
1,25-DHCC	1,25-dihydroxycholecalciferol
17-OHP	17α-hydroxyprogesterone
^{201}TI	thallium-201
2,3 DPG	2,3-diphosphoglycerate
25-HCC	25-hydroxycholecalciferol
3SR	self-sustained sequence replication
5HT	serotonin
6-AM	6-acetylmorphine
6MWT	6-minute walk test
^{99m}Tc	technetium-99m
^{201}Tl	thallium-201 (radio isotope)
α_1AC	α1-antichymotrypsin
A-G6PD	glucose-6 phosphate dehydrogenase variant
A1c	glycosylated hemoglobin
A2M, α2M	α2-macroglobulin
AACE	American Association of Clinical Endocrinologists
AAG	α1-acid glycoprotein
ABG	arterial blood gas
ACA	anticentromere antibody
ACC	American College of Cardiology
ACCF	American College of Cardiology Foundation
ACCP	American College of Clinical Pharmacy
ACCP	anticyclic citrullinated peptide
ACE	angiotensin-converting enzyme
ACE-I	angiotensin-converting enzyme inhibitor
ACPA	anticitrullinated protein antibody
ACR	albumin-to-creatinine ratio; American College of Rheumatology
ACS	acute coronary syndrome
ACT	activated clotting time; α1-coded testing
ACTH	adrenocorticotropic hormone (corticotropin)
ADA	American Diabetes Association
ADAM	androgen deficiency in aging males
ADCC	antibody-dependent cellular cytotoxicity
ADH	antidiuretic hormone
ADME	absorption, distribution, metabolism, excretion
ADP	adenosine diphosphate
AFB	acid-fast bacilli
AFP	α-fetoprotein
AG	anion gap
AGPA	allergic granulomatosis with polyangiitis
AHA	American Heart Association
AIDS	acquired immunodeficiency syndrome
ALK	anaplastic lymphoma kinase
ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMA	antimitochondrial antibody
AMI	acute myocardial infarction
AML	acute myelogenous leukemia
ANA	antinuclear antibody
ANCA	antineutrophil cytoplasmic antibody
ANF	atrial natriuretic factor
ANP	atrial natriuretic peptide
anti-HAV IgG	IgG antibody against hepatitis A virus
anti-HAV IgM	IgM antibody against hepatitis A virus
anti-HBc	antibody to hepatitis B core antigen
anti-HbeAg	antibody to hepatitis B extracellular antigen
anti-HBs	antibody to hepatitis B surface antigen
anti-HCV	antibody against HCV antigen
anti-HD	antibody against hepatitis D
APC	activated protein C
APC	antigen-presenting cell
apoB	apolipoprotein B
APS	antiphospholipid antibody syndrome
aPTT	activated partial thromboplastin time
ARB	angiotensin receptor blocker
ASA	aspirin
ASCO	American Society of Clinical Oncology
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate aminotransferase
AT	antithrombin
ATP	adenosine triphosphate
ATP-K	adenosine triphosphate potassium
ATP	Adult Treatment Panel
ATP III	Adult Treatment Panel III
ATS	American Thoracic Society
AUA	American Urological Association
AUA-SI	American Urological Association Symptom Index
AUC	area under the (serum concentration time) curve
AV	atrioventricular
AVP	arginine vasopressin
B&B	Brown and Brenn
B2M	β2-microglobulin
BAL	bronchial alveolar lavage; bronchoalveolar lavage
BAMT	blood assay for *Mycobacterium tuberculosis*
BBT	basal body temperature
BCG	Bacillus Calmette-Guérin
bDNA	branched-chain DNA

BGMK-hDAF	buffalo green monkey kidney cell line decay accelerating factor
BHI	brain heart infusion
BHR	bronchial hyper-responsiveness
BID	twice daily
BMI	body mass index
BMP	basic metabolic panel
BNP	brain natriuretic peptide
BP	blood pressure
BPH	benign prostatic hyperplasia
BPSA	benign form of prostate-specific antigen
BPT	bronchial provocation testing
BRAF	v-Raf murine sarcoma viral oncogene homolog B1
BSA	body surface area
BSL	biosafety level
BT	bleeding time
BUN	blood urea nitrogen
C. difficile	*Clostridium difficile*
C3	complement protein 3
C4	complement protein 4
CA	cancer antigen
CA	carbonic anhydrase
CABG	coronary artery bypass graft
CA_{corr}	corrected serum calcium level
CAD	coronary artery disease
CAH	congenital adrenal hyperplasia
CAN2	chromID Candida agar
cANCA	cytoplasmic antineutrophil cytoplasmic antibody
CAP	College of Pathologists
CAP	community-acquired pneumonia
CAT	computerized axial tomography
CA_{uncorr}	uncorrected serum calcium level (or actual measured total serum calcium)
CBC	complete blood count
CCFA	cycloserine cefoxitin fructose agar
CCNA	cell cytotoxicity neutralization assay
CCP	cyclic citrullinated peptide
CCR5	chemokine coreceptor 5
cCRP	cardiac C-reactive protein
CCT	cardiac computed tomography
cd	candela
CD	clusters of differentiation
CDC	Centers for Disease Control and Prevention
CDR	complementarity-determining regions
CE	capillary electrophoresis
CEA	carcinoembryonic antigen
CEDIA	cloned enzyme donor immunoassay
CETP	cholesteryl ester transfer protein
CF	complement fixation
CFTR	cystic fibrosis transmembrane conductance regulator
CFU, cfu	colony-forming units
CFW	calcofluor white
CGE	capillary gel electrophoresis
CH_{50}	complement hemolytic 50%
CHD	coronary heart disease
CHF	congestive heart failure
CI	chemical ionization
CIS	combined intracavernous injection and stimulation
CK	creatine kinase
CK-BB	creatine kinase isoenzyme BB
CK-MB	creatine kinase isoenzyme MB
CK-MM	creatine kinase isoenzyme MM
CK1	creatine kinase isoenzyme 1
CK2	creatine kinase isoenzyme 2
CK3	creatine kinase isoenzyme 3
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CLIA-88	Clinical Laboratory Improvement Amendments of 1988
CLIA	Clinical Laboratory Improvement Amendments
CLL	chronic lymphocytic leukemia
CLSI	Clinical and Laboratory Standards Institute
cm	centimeter
CMA	cornmeal agar
C_{min}	minimum concentration (of a drug)
CML	chronic myelogenous leukemia
CMP	comprehensive metabolic panel
CMR	cardiac magnetic resonance
CMV	cytomegalovirus
CNA	colistin-nalidixic acid
$C_{normalized}$	normalized total concentration
CNP	c-type natriuretic peptide
CNS	central nervous system
CO	carbon monoxide; cardiac output; cyclooxygenase
CO_2	carbon dioxide
CO-Hgb	carboxyhemoglobin
COP	colloid osmotic pressure
COPD	chronic obstructive pulmonary disease
CPE	cytopathic effect
CPK	creatine phosphokinase
CPPD	calcium pyrophosphate dihydrate
cPSA	complexed PSA
CrCl	creatinine clearance
CREST	syndrome characterized by **c**alcinosis, **R**aynaud disease, **e**sophageal motility disorder, **s**clerodactyly, and **t**elangiectasias
CRH	corticotrophin-releasing hormone
CRP	C-reactive protein
CSF	cerebrospinal fluid
$C_{ss, avg}$	average steady-state concentration (of a drug)
CT	computed tomography
cTnC	cardiac-specific troponin C
cTnI	cardiac-specific troponin I

cTnT	cardiac-specific troponin T
CVD	cardiovascular disease
CX	circumflex
CXCR4	CXC chemokine coreceptor
CYP	cytochrome P450 drug metabolizing enzymes
CYP2C19	cytochrome P450 2C19 enzyme
CYP2D6	cytochrome P450 2D6 enzyme
CYP3A4	cytochrome P450 3A4 enzyme
CYP450	cytochrome P450 enzyme
CYP4F2	cytochrome P450 4F2 enzyme
CZE	capillary zone electrophoresis
D&C	dilation and curettage
D5W	5% dextrose in water
DASH	**d**ietary **a**pproaches to **s**top **h**ypertension
DAT	direct agglutination test
DAT	direct antibody test
DCCT	Diabetes Control and Complications Trial
DCP	des-gamma-carboxyprothrombin
DDAVP	desmopressin
dTT	dilute thrombin time
DDT	dichlorodiphenyltrichloroethane
DFA	direct fluorescent antibody
DHA	docosahexaenoic acid
DHEA	dehydroepiandrostenedione or dehydroepiandrosterone
DHEAS	dehydroepiandrosterone sulfate
DI	diabetes insipidus
DIC	disseminated intravascular coagulation
DIM	dermatophyte identification medium
DKA	diabetic ketoacidosis
dL	deciliter
DLCO	diffusing capacity of the lung for carbon monoxide
DM	diabetes mellitus
DNA	deoxyribonucleic acid
DNP	dendroaspis natriuretic peptide
DO_2	oxygen delivery
DOAC	direct oral anticoagulant
DPD	dihydropyrimidine dehydrogenase
DPP-4	dipeptidyl peptidase-4
dsDNA	double-stranded DNA
DST	dexamethasone suppression test
DTI	direct thrombin inhibitor
DTM	dermatophyte test medium
E2	estradiol
EBM	esculin base medium
EBV	Epstein-Barr virus
ECD	energy coupled dye
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
ECT	ecarin clotting time
ECW	extracellular water
ED	emergency department
EDTA	ethylenediaminetetraacetic acid
EGFR	epidermal growth factor receptor
eGFR	estimated glomerular filtration rate
EF	ejection fraction
EI	electron ionization
EIA	enzyme immunoassay
EIB	exercise- or exertion-induced bronchospasm
EKG	electrocardiogram
ELISA	enzyme-linked immunosorbent assay
ELVIS	enzyme-linked virus-inducible system
EM	electron microscopy
EMB	eosin methylene blue
EMIT	enzyme-multiplied immunoassay technique
EOF	electroosmotic force
EPA	eicosapentaenoic acid
EPS	expressed prostatic secretions
ER	estrogen receptor
ERS	European Respiratory Society
ERV	expiratory reserve volume
ESA	erythrocyte-stimulating agent
ESBL	extended-spectrum β-lactamase
ESC	European Society of Cardiology
ESI	electrospray ionization
ESR	erythrocyte sedimentation rate
ESRD	end-stage renal disease
Etest	epsilometer test
ETIB	enzyme-linked immunoelectrotransfer blot
EU	ELISA units
EUCAST	European Committee on Antimicrobial Susceptibility Testing
EULAR	European League Against Rheumatism
FA	fluorescent antibody
Fab	fraction antigen-binding
FAB	fast atom bombardment
FAB	French-American-British
FACS	fluorescence-activated cell sorting
FALS	forward-angle light scattering
FANA	fluorescent antinuclear antibody
FDA	Food and Drug Administration
FDP	fibrin degradation product
$FEF_{25–75}$	forced expiratory flow at 25% to 75% of vital capacity
FEF	forced expiratory flow
FE_{Na}	fractional excretion of sodium
FENO	fractional exhaled nitric oxide
FEV_1	forced expiratory volume in 1 second
FiO_2	fraction of inspired oxygen
FISH	fluorescence in situ hybridization
FITC	fluorescein isothiocyanate
fL	femtoliter
FM	Fontana-Masson
FN	false negative
FP	false positive
FPG	fasting plasma glucose
FPIA	fluorescence polarization immunoassay

fPSA	free prostate specific antigen
FRC	functional residual capacity
FSH	follicle-stimulating hormone
FTA-ABS	fluorescent treponemal antibody absorption
FVC	forced vital capacity
FWR	framework regions
g	gram
G-CSF	granulocyte colony–stimulating factor
G6PD	glucose-6 phosphate dehydrogenase
GA	gestational age
GADA	glutamic acid decarboxylase autoantibodies
GAP	group A streptococcus
GAS	group A streptococci
GC	gas chromatography
GC-MS	gas chromatography and mass spectrometry
GERD	gastroesophageal reflux disease
GF	Gridley fungus
GFR	glomerular filtration rate
GGT, GGTP	gamma-glutamyl transferase; gamma-glutamyl transpeptidase
GHB	gamma-hydroxybutyrate
GI	gastrointestinal
GIP	glucose-dependent insulinotropic peptide
GLC	gas liquid chromatography
GLP-1	incretin hormones glucagon-like peptide-1
GLUT	glucose transporter
GM-CSF	granulocyte/macrophage colony-stimulating factor
GMS	Gomori methenamine silver
GnRH	gonadotropin-releasing hormone
GOLD	Global Initiative for Chronic Obstructive Lung Disease
gp	glycoprotein
GPA	granulomatosis with polyangiitis
GTF	glucose tolerance factor
H&E	hematoxylin and eosin
H. Pylori	*Helicobacter pylori*
HAAg	hepatitis A antigen
HAP	hospital-acquired pneumonia
HAV	hepatitis A virus
Hb; hgb	hemoglobin
HbA1c	glycated hemoglobin
HBcAg	hepatitis B core antigen
HBeAg	hepatitis B extracellular antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCO_3^-	bicarbonate
HCT, Hct	hematocrit
HCV	hepatitis C virus
HDAg	hepatitis D antigen
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
HDV	hepatitis D virus
HER-1	human epidermal growth factor receptor 1
HER-2	human epidermal growth factor receptor 2
HEV	hepatitis E virus
HF*p*EF	heart failure with preserved ejection fraction
HF*r*EF	heart failure with reduced ejection fraction
HGA	human granulocytic anaplasmosis
Hgb	hemoglobin
HHS	hyperosmolar hyperglycemic state
HIPA	heparin-induced platelet activation
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HLA	human leukocyte antigen
HLA-B27	human leukocyte antigen B27
HLA-DQ	human leukocyte antigen coded DQ genes
HLAR	high-level aminoglycoside resistance
HME	human monocytic ehrlichiosis
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
HMWK	high-molecular weight kininogen
HPA	hypothalamic pituitary axis
HPF	high-power field
HPLC	high-performance (or pressure) liquid chromatography
HPV	human papillomavirus
HR	heart rate
hr	hour
hs-CRP	high-sensitivity C-reactive protein
HSG	hysterosalpingogram, hysterosalpingography
hsTnI	high-sensitivity troponin I
hsTnT	high-sensitivity troponin T
HSV	herpes simplex virus
Ht	height
HTN	hypertension
I	intermediate
IA	immunoassay
IA-2A	insulinoma-associated-2 autoantibodies
IAA	insulin autoantibodies
IAT	indirect antibody test
IBW	ideal body weight
IC	inspiratory capacity
IC_{50}	inhibitory concentration 50%
IC_{90}	inhibitory concentration 90%
ICA	immunochromatographic assay
ICA	islet cell cytoplasmic autoantibodies
ICTV	International Committee on Taxonomy of Viruses
ICU	intensive care unit
ICW	intracellular water
ID	immunodiffusion
IDC	International Diabetes Center
IDL	intermediate-density lipoproteins
IDMS	isotope dilution mass spectrometry
IFA	immunofluorescence assay; indirect fluorescent antibody

IFN-γ	interferon gamma
IgA	immunoglobulin A
IgD	immunoglobulin D
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
IHC	immunohistochemistry
IHD	ischemic heart disease
IIEF	International Index of Erectile Function
IIM	idiopathic inflammatory myopathy
IMA	inhibitory mold agar
INR	international normalized ratio
IP	interphalangeal
iPSA	inactive PSA
IPSS	International Prostate Symptom Score
IQ	inhibitory quotient
IRMA	immunoradiometric assay
IRV	inspiratory reserve volume
ISE	ion-selective electrode
ISI	International Sensitivity Index
ITP	idiopathic thrombocytopenic purpura
IV	intravenous
J	joule
JIA	juvenile idiopathic arthritis
JRA	juvenile rheumatoid arthritis
JVP	jugular venous pressure
k	constant of proportionality
K	kelvin
K_{corr}	corrected serum potassium level
KDIGO	Kidney Disease Improving Global Outcomes
kg	kilogram
KIMS	kinetic interaction of microparticles in solution
Km	Michaelis constant
KOH	potassium hydroxide
KRas	V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
K_{uncorr}	uncorrected serum potassium level (or actual measured serum potassium)
L	liter
LA	latex agglutination
La/SSB	La/Sjögren syndrome B
LAD	left anterior descending
LBBB	left bundle branch block
LC	liquid chromatography
LCAT	lecithin cholesterol acyltransferase
LCR	ligase chain reaction
LDH	lactate dehydrogenase
LDH1	lactate dehydrogenase isoenzyme 1
LDH2	lactate dehydrogenase isoenzyme 2
LDH3	lactate dehydrogenase isoenzyme 3
LDH4	lactate dehydrogenase isoenzyme 4
LDH5	lactate dehydrogenase isoenzyme 5
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LE	lupus erythematosus
LFT	liver function test
LH	luteinizing hormone
LHRH	luteinizing hormone–releasing hormone
LIS	laboratory information system
LMP	last menstrual period
LMWH	low molecular weight heparin
Lp(a)	lipoprotein(a)
Lp-PLA_2	lipoprotein-associated phospholipase A_2
LPL	lipoprotein lipase
LSD	lysergic acid diethylamide
LTA	light transmittance aggregometry
LUTS	lower urinary tract symptoms
LVEF	left ventricular ejection fraction
m	meter
m^2	meters squared
MAbs	monoclonal antibodies
Mac	MacConkey
MAC	membrane attack complex
MAC	*Mycobacterium avium* complex
MALDI	matrix-assisted laser desorption/ionization
MALDI-TOF	matrix-assisted laser desorption ionization time-of-flight
MAP	mitogen-activated protein
MAT	microagglutination test
MBC	minimum bactericidal concentration
MBP	mannose-binding protein
mcg	microgram
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCP	metacarpophalangeal
MCT	medium chain triglycerides
MCTD	mixed connective tissue disease
MCV	mean corpuscular volume
MDMA	3,4-methylenedioxy-N-methamphetamine (Ecstasy)
MDR	multidrug resistant
MDRD	Modification of Diet in Renal Disease
MDx	molecular diagnostics
mEq	milliequivalent
mg	milligram
MHA	Mueller-Hinton agar
MHA-TP	microhemagglutination *Treponema pallidum*
MHC	major histocompatibility complex
MI	myocardial infarction
MIC	minimum inhibitory concentration
MIC_{50}	MIC value representing 50% of a bacterial population
MIC_{90}	MIC value representing 90% of a bacterial population
MIF	microimmunofluorescence
min	minute

mL	milliliter
mm	millimeter
mm^3	cubic millimeter
mmol	millimole
mTOR	mammalian target of rapamycin
moAb	monoclonal antibody
mol	mole
MOTT	mycobacteria other than tuberculosis
MPO	myeloperoxidase
MPV	mean platelet volume
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MRO	medical review officer
MRP1	multidrug resistant protein 1
MRP2	multidrug resistant protein 2
MRP3	multidrug resistant protein 3
MRSA	methicillin-resistant *Staphylococcus aureus*
MS	mass spectrometry
MSSA	methicillin-susceptible *Staphylococcus aureus*
mTOR	mammalian (or mechanistic) target of rapamycin
MTP	metatarsophalangeal
N	newton
NA	nucleic acid
NAAT	nucleic acid amplification test
NACB	National Academy of Clinical Biochemistry
NAEPP	National Asthma Education Prevention Program
NASBA	nucleic acid sequence-based amplification
NASH	nonalcoholic steatohepatitis
NCCB	nondihydropyridine calcium channel blocker
NCEP	National Cholesterol Education Program
ng	nanogram
NHL	Non-Hodgkin lymphoma
NK cells	natural killer (T) lymphocytes
NKDEP	National Kidney Disease Education Program
NKF KDOQI	National Kidney Foundation Kidney Disease Outcomes Quality Initiative
NLA	National Lipid Association
nm	nanometer
NNRTI	non-nucleoside reverse transcriptase inhibitor
NNS	number needed to screen
NQO1	NADPH quinone dehydrogenase 1
NQMI	non Q-wave myocardial infarction
NRTI	nucleoside reverse transcriptase inhibitor
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small-cell lung cancer
NSTEMI	non-ST-segment elevation myocardial infarction
NT-proBNP	N-terminal-proBNP
NTM	nontuberculous mycobacteria
NYHA	New York Heart Association
OA	osteoarthritis
OAT	organic anion transport
OATP1	organic anion-transporting polypeptide 1
OATP2	organic anion-transporting polypeptide 2
OCT	organic cation transport
OGTT	oral glucose tolerance test
OSHA	Occupational Safety and Health Administration
$P_1G_1O_1$	one live birth, one pregnancy, no spontaneous or elective abortions
P-gp	P-glycoprotein
Pa	Pascal
pAB	polyclonal antibody
$PaCO_2$	partial pressure of carbon dioxide, arterial
PAD	peripheral arterial disease
PAE	postantibiotic effect
PAI1	plasminogen activator inhibitor 1
pANCA	perinuclear antineutrophil cytoplasmic antibody
PaO_2	partial pressure of oxygen, arterial
PAS	periodic acid-Schiff
PBC	primary biliary cirrhosis
PBMC	peripheral blood mononuclear cell
PBP	penicillin-binding protein
$PC_{20}FEV_1$	provocation concentration of the bronchoconstrictor agent that produces a 20% reduction in FEV_1
PCA	postconceptional age
PCI	percutaneous coronary intervention
pCO_2	partial pressure of carbon dioxide
PCOS	polycystic ovary syndrome
PCP	phencyclidine
PCR	polymerase chain reaction
PCSK9	proprotein convertase subtilisin/kexin type 9
PD	pharmacodynamic
PDA	potato dextrose agar
PE	phycoerythrin
$Peak_{steady\ state}$	Peak concentration of a drug in serum or plasma
PEA	phenylethyl alcohol
PEFR	peak expiratory flow rate
PET	positron emission tomography
PF3	platelet factor 3
PF4	platelet factor 4
PFA	potato flake agar
PFGE	pulsed-field gel electrophoresis
PFT	pulmonary function test
pg	picogram
PG	prostaglandin
PG2	prostacyclin
pH	power of hydrogen or hydrogen ion concentration
PHY	phenytoin

Ph	Philadelphia
PICU	pediatric intensive care unit
PID	pelvic inflammatory disease
PIP	proximal interphalangeal
PK	pharmacokinetic
PKU	phenylketonuria
PL	phospholipid
PMA	postmenstrual age
PMN	polymorphonuclear leukocyte
PNA	postnatal age
PNA-FISH	peptide nucleic acid fluorescent in situ hybridization
PO	per os (by mouth)
pO_2	partial pressure of oxygen
POC	point-of-care
POCT	point-of-care testing
PPAR	peroxisome proliferator-activated receptor
PPD	purified protein derivative
PPG	postprandial glucose
PPI	proton pump inhibitor
PR	progesterone receptor
PR3	proteinase 3
PRN	as needed
PRU	P2Y12 reaction units
PSA	prostate specific antigen
PSAD	prostate specific antigen density
PSB	protected specimen brush
PSM	patient self-management
PST	patient self-testing
PT	prothrombin time
PTCA	percutaneous transluminal coronary angioplasty
PTH	parathyroid hormone
q	every
Q	perfusion
QC	quality control
QID	four times daily
qPCR	real-time polymerase chain reaction
QRS	electrocardiograph wave; represents ventricular depolarization
QwMI	Q-wave myocardial infarction
R	resistant
R-CVA	right cerebral vascular accident
RA	rheumatoid arthritis
RAAS	renin-angiotensin-aldosterone system
RADT	rapid antigen detection test
RAEB	refractory anemia with excess blasts
RAIU	radioactive iodine uptake test
RALS	right-angle light scattering
RBC	red blood cell
RBF	renal blood flow
RCA	right coronary artery
RDW	red cell distribution width
RF	rheumatoid factor
RhMK	rhesus monkey kidney
RI	reticulocyte index
RIA	radioimmunoassay
RIBA	recombinant immunoblot assay
RIDTs	rapid influenza diagnostic tests
RNA	ribonucleic acid
RNP	ribonucleoprotein
Ro/SSA	Ro/Sjögren syndrome A antibody
RPF	renal plasma flow
RPR	rapid plasma reagin
RR	respiratory rate
RSA	rapid sporulation agar
RSAT	rapid streptococcal antigen test
RSV	respiratory syncytial virus
RT	reverse transcriptase; reverse transcription
RT-PCR	reverse-transcriptase polymerase chain reaction
RV	residual volume
S	susceptible
S Cys C	serum cystatin C
S:P ratio	saliva:plasma concentration ratio
SA	sinoatrial
SaO_2	arterial oxygen saturation
SAMHSA	Substance Abuse and Mental Health Services Administration
SAT	serum agglutination test
SBA	sheep blood agar
SBT	serum bactericidal test
Scl_{70}	scleroderma-70 or DNA topoisomerase I antibody
SCr	serum creatinine
$ScvO_2$	central venous oxygen saturation
SD	standard deviation
SDA	Sabouraud dextrose agar
SDA	strand displacement amplification
sec	second
SEGA	subependymal giant cell astrocytoma
SGE	spiral gradient endpoint
SGLT	sodium glucose cotransporters
SHBG	sex hormone-binding globulin
SI	International System of Units
SIADH	syndrome of inappropriate antidiuretic hormone
SID	strong iron difference
SIG	strong ion gap
SLE	systemic lupus erythematosus
Sm	Smith antibody
SMBG	self-monitoring blood glucose
SNP	single nucleotide polymorphism
SNRI	serotonin–norepinephrine reuptake inhibitor
SnRNP	small nuclear ribonucleoprotein particle
SPECT	single-photon emission computed tomography
SPEP	serum protein electrophoresis
SRA	C-serotonin release assay

ssDNA	single-stranded DNA
SSRI	selective serotonin reuptake inhibitor
STD	sexually transmitted disease
STEMI	ST segment elevation myocardial infarction
SV	stroke volume
SVC	slow vital capacity
SvO_2	venous oxygen saturation
T_3	triiodothyronine
T_3RU	triiodothyronine resin uptake
T_4	thyroxine
TAT	turnaround time
TB	tuberculosis
TBG	thyroxine-binding globulin
TBI	total body irradiation
TBPA	thyroid-binding prealbumin
TBW	total body water
TBW	total body weight
TC	total cholesterol
TCA	tricyclic antidepressant
TDM	therapeutic drug monitoring
TEE	transesophageal echocardiography
TF	tissue factor
TFPI	tissue factor pathway inhibitor
TG	triglyceride
THC	total hemolytic complement
TIA	transient ischemic attack
TIBC	total iron-binding capacity
TID	three times daily
TJC	The Joint Commission
TK	tyrosine kinase
TKI	tyrosine kinase inhibitor
TLA	total laboratory automation
TLC	therapeutic lifestyle changes
TLC	thin layer chromatography
TLC	total lung capacity
TMA	transcription mediated amplification
TN	true negative
TnC	troponin C
TNF	tumor necrosis factor
TnI	troponin I
TnT	troponin T
TP	true positive; tube precipitin
tPA	tissue plasminogen activator
TPMT	thiopurine methyltransferase
TPN	total parenteral nutrition
TR	therapeutic range
TRH	thyrotropin-releasing hormone
TRUS	transrectal ultrasound of the prostate
TSB	trypticase soy broth
TSH	thyroid-stimulating hormone
TST	tuberculin skin test
TT	thrombin time
TTE	transthoracic echocardiography
TTP	thrombotic thrombocytopenic purpura; total testing process
TTR	time in therapeutic range
TV	tidal volume
T_XA_2	thromboxane A_2
type 1 DM	type 1 diabetes mellitus
type 2 DM	type 2 diabetes mellitus
U	urinary creatinine concentration
U_1RNP	uridine-rich ribonuclear protein
UA	unstable angina
UCr	urine creatinine
UFC	urine-free cortisol
UFH	unfractionated heparin
UGT1A1	uridine diphosphate glucuronyl transferase
UKPDS	United Kingdom Prospective Diabetes Study
ULN	upper limit of normal
uNGAL	urine neutrophil gelatinase associated lipocalcin
uPA	urokinase plasminogen activator
UTI	urinary tract infection
UV	ultraviolet
V	total urine volume collected; ventilation; volt
VAP	ventilator-associated pneumonia
VC	vital capacity
Vd	volume of distribution
VDRL	Venereal Disease Research Laboratory
VISA	vancomycin-intermediate *Staphylococcus aureus*
VKORC1	vitamin K epoxide reductase complex subunit 1
VLDL	very low-density lipoprotein
V_{max}	maximum rate of metabolism
VPA	valproic acid
VO_2	oxygen consumption
VRE	vancomycin-resistant enterococci
VTE	venous thromboembolism
vWF	von Willebrand factor
VZV	varicella zoster virus
W	watt
WB	western blot
WBC	white blood cell
WHO	World Health Organization
WNL	within normal limits
Wt	weight
WT	wild type
yr	year

PART I

BASIC CONCEPTS AND TEST INTERPRETATIONS

1 DEFINITIONS AND CONCEPTS

Karen J. Tietze

OBJECTIVES

After completing this chapter, the reader should be able to

- Differentiate between accuracy and precision
- Distinguish between quantitative, qualitative, and semiqualitative laboratory tests
- Define reference range and identify factors that affect a reference range
- Differentiate between sensitivity and specificity, and calculate and assess these parameters
- Identify potential sources of laboratory errors and state the impact of these errors in the interpretation of laboratory tests
- Identify patient-specific factors that must be considered when assessing laboratory data
- Discuss the pros and cons of point-of-care and at-home laboratory testing
- Describe a rational approach to interpreting laboratory results

Laboratory testing is used to detect disease, guide treatment, monitor response to treatment, and monitor disease progression. However, it is an imperfect science. Laboratory testing may fail to identify abnormalities that are present (false negatives [FNs]) or identify abnormalities that are not present (false positives [FPs]). This chapter defines terms used to describe and differentiate laboratory tests and describes factors that must be considered when assessing and applying laboratory test results.

DEFINITIONS

Many terms are used to describe and differentiate laboratory test characteristics and results. The clinician should recognize and understand these terms before assessing and applying test results to individual patients.

Accuracy and Precision

Accuracy and *precision* are important laboratory quality control measures. Laboratories are expected to test analytes with accuracy and precision and to document the quality control procedures. Accuracy of a quantitative assay is usually measured in terms of analytical performance, which includes accuracy and precision. *Accuracy* is defined as the extent to which the mean measurement is close to the true value. A sample spiked with a known quantity of an analyte is measured repeatedly; the mean measurement is calculated. A highly accurate assay means that the repeated analyses produce a mean value that is the same as or very close to the known spiked quantity. Accuracy of a qualitative assay is calculated as the sum of the true positives (TPs) and true negatives (TNs) divided by the number of samples tested (accuracy = [(TP + TN) ÷ number of samples tested] × 100%). *Precision* refers to assay reproducibility (i.e., the agreement of results when the specimen is assayed many times). An assay with high precision means the methodology is consistently able to produce results in close agreement. The accuracy of those results is a separate issue.

Analyte

The *analyte* is the substance measured by the assay. Some substances, such as phenytoin and calcium, are bound extensively to proteins such as albumin. Although the unbound fraction elicits the physiological or pharmacological effect (bound substances are inactive), most routine assays measure the total substance (bound plus unbound). The free fraction may be assayable, but the assays are not routine. Therefore, the reference range for total and free substances may be quite different. For example, the reference range is 10–20 mcg/mL for total phenytoin, 1–2 mcg/mL for free phenytoin, 9.2–11 mg/dL for total serum calcium, and 4–4.8 mg/dL for free (also called *ionized*) calcium.

Some analytes exist in several forms and each has a different reference range. These forms are referred to as *fractions, subtypes, subforms, isoenzymes*, or *isoforms*.

Note: This chapter is based, in part, on the second edition chapter titled "Definitions and Concepts" by Scott L. Traub.

Results for the total and each form are reported. For example, bilirubin circulates in conjugated and unconjugated subforms as well as bound irreversibly to albumin (delta bilirubin). *Direct bilirubin* refers to the sum of the conjugated plus the delta forms (water soluble forms); *indirect bilirubin* refers to the unconjugated form (water insoluble form). Lactate dehydrogenase (LDH) is separated electrophoretically into five different isoenzymes: LDH1, LDH2, LDH3, LDH4, and LDH5. Creatine kinase (CK) exists in three isoforms: CK-BB (CK1), CK-MB (CK2), and CK-MM (CK3).

Biomarker

A *biomarker* (biological marker) is a marker (not necessarily a quantifiable laboratory parameter) defined by the National Institutes of Health as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."[1] Biomarkers are used to diagnose and stage disease (i.e., determine the extent of disease), assess disease progression, and predict or assess response to therapeutic interventions. Tumor markers are biomarkers used to identify the presence of some cancers, to stage disease, or to assess patient response to drug and nondrug cancer treatments. Many biomarkers are common laboratory parameters. For example, glycated hemoglobin A1c (HbA1c) is used to assess long-term glucose control in patients with diabetes.

Noninvasive Versus Invasive Tests

A *noninvasive test* is a procedure that examines fluids or other substances (e.g., urine and exhaled air) obtained without using a needle, tube, device, or scope to penetrate the skin or enter the body. An *invasive test* is a procedure that examines fluids or tissues (e.g., venous blood and skin biopsy) obtained by using a needle, tube, device, or scope to penetrate the skin or enter the body. Invasive tests pose variable risk depending on the method of specimen collection (e.g., pain and bruising associated with venipuncture) and are less convenient than noninvasive tests.

Predictive Value

The *predictive value*, derived from a test's sensitivity, specificity, and prevalence (incidence) of the disease in the population being tested, is used to assess a test's reliability (**Table 1-1**). As applied to a positive test result, the predictive value indicates the percent of positives that are TPs. For a test with equal sensitivity and specificity, the predictive value of a positive result increases as the incidence of the disease in the population increases. For example, the glucose tolerance test has a higher predictive value for diabetes in women who are pregnant than in the general population. A borderline abnormal serum creatinine (SCr) concentration has a higher predictive value for kidney disease in patients in a nephrology unit than in patients in a general medical unit. The lower the prevalence of disease in the population tested, the greater the chance that a positive test result is in error. The predictive value may also be applied to negative results. As applied to a negative test result, the predictive value indicates the percent of negatives that are TNs (**Minicase 1**).

TABLE 1-1. Relationship of Sensitivity, Specificity, Disease Prevalence, and Predictive Value of Positive Test[a,b]

SENSITIVITY AND SPECIFICITY (%)	PREVALENCE (%)	PREDICTIVE VALUE OF POSITIVE TEST (%)
95	0.1	1.9
	1	16.1
	2	27.9
	5	50
	50	95
99	0.1	9
	1	50
	2	66.9
	5	83.9
	50	99

[a]The predictive value of a positive test increases as the disease prevalence and sensitivity and specificity of the test increase.
[b]Predictive value of positive test = [TP ÷ (TP + FP)] x 100%. Predictive value of negative test = [TN ÷ (TN + FN)] x 100%. Disease prevalence = (TP + FN) ÷ number of patients tested. FN = diseased persons not detected by test (false negatives); FP = nondiseased persons positive to test (false positives); TN = nondiseased persons negative to test (true negatives); and TP = diseased persons detected by test (true positives).

Qualitative Tests

A *qualitative test* is a test whose results are reported as either positive or negative without further characterization of the degree of positivity or negativity. Exact quantities may be measured in the laboratory but are still reported qualitatively using predetermined ranges. For example, a serum or urine pregnancy test is reported as either positive or negative; a bacterial wound culture is reported as either positive for one or more specific microorganisms or reported as no growth; a urine toxicology drug screen is reported as either positive or negative for specific drugs; a hepatitis C viral ribonucleic acid (RNA) test is reported as positive or negative for hepatitis C viral RNA; and an acid-fast stain for *Mycobacterium* is reported as either positive or negative.

Quantitative Tests

A *quantitative test* is a test whose results are reported as an exact numeric measurement (usually a specific mass per unit measurement) and assessed in the context of a reference range of values. For example, serum potassium is reported in milliequivalents per liter, creatinine clearance (CrCl) is reported in milliliters per minute, and LDH is reported in units per liter. Some test results are reported as titers (dilutions). A serum antinuclear antibody titer of 1:160 is usually associated with active systemic lupus erythematosus or other autoimmune diseases, although some patients may have "low titer" disease with titers of 1:40 or 1:80.

MINICASE 1

Rapid Streptococcal Antigen Test

In 453 patients with acute pharyngitis symptoms, detection of group A β-hemolytic streptococci with a commercial rapid antigen detection test and standard throat culture are compared.[2] The package insert for the rapid streptococcal antigen test (RSAT) notes a sensitivity of 95% and a specificity of 98% when used according to the manufacturer instructions.

QUESTION: After reviewing the following results, what conclusions can be made about the clinical performance of the RSAT?

RSAT Results (*n* = 453):

True Positives	51	True Negatives	362
False Positives	12	False Negatives	28

DISCUSSION: Calculate sensitivity, specificity, predictive value of a positive test, and the predictive value of a negative test.

Sensitivity = (TP ÷ [TP + FN]) × 100% = (51 ÷ [51 + 28]) × 100% = 64.6%

Specificity = (TN ÷ [TN + FP]) × 100% = (362 ÷ [362 + 12]) × 100% = 96.8%

Predictive value of positive test = (TP ÷ [TP + FP]) × 100% = (51 ÷ [51 + 12]) × 100% = 81%

Predictive value of negative test = (TN ÷ [TN + FN]) × 100% = (362 ÷ [362 + 28]) × 100% = 92.8%

In this study, RSAT has a lower specificity and sensitivity than reported by the manufacturer; the sensitivity depends on proper throat swab collection. Appropriate healthcare training is important to achieve and maintain maximum sensitivity and positive predictive value of the test.

Reference Range

The *reference range* (also known as the *reference interval* or the *reference value*) is a statistically-derived numerical range obtained by testing a sample of individuals assumed to be healthy. The upper and lower limits of the range are not absolute (i.e., normal versus abnormal) but rather points beyond which the probability of clinical significance begins to increase. The term *reference range* is preferred over the term *normal range*.[3] The reference population is assumed to have a Gaussian distribution with 68% of the values within one standard deviation (SD) above and below the mean, 95% within ±2 SD, and 99.7% within ±3 SD (**Figure 1-1**).

The reference range for a given analyte is usually established in the clinical laboratory as the mean or average value plus or minus two SDs. Acceptance of the mean ±2 SD indicates that one in 20 normal individuals will have test results outside the reference range (2.5% have values below the lower limit of the reference range, and 2.5% have values above the upper limit of the reference range). Accepting a wider range (e.g., ±3 SD) includes a larger percentage (99.7%) of normal individuals but increases the chance of including individuals with values only slightly outside of a more narrow range, thus decreasing the sensitivity of the test.

Qualitative laboratory tests are either negative or positive and without a reference range; any positivity is considered abnormal. For example, any amount of serum acetone, porphobilinogen, or alcohol in serum or plasma is considered abnormal. The presence of glucose, ketones, blood, bile, or nitrate in urine is also abnormal. The results of the VDRL (Veneral Disease Research Laboratory) test, tests for red blood cell (RBC) sickling, and the malaria smear are either positive or negative.

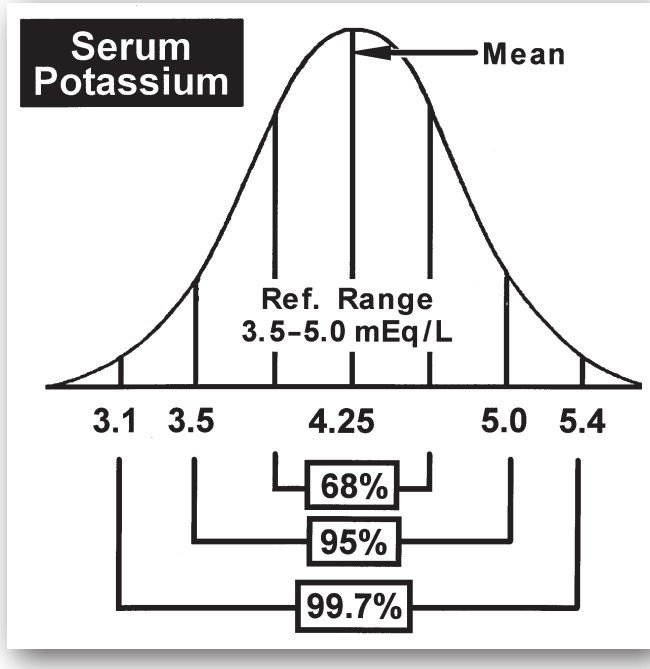

FIGURE 1-1. Gaussian (random) value distribution with a visual display of the area included within increments of standard deviation (SD) above and below the mean: ±1 SD = 68% of total values; ±2 SD = 95% of total values; and ±3 SD = 99.7% of total values.

Factors That Influence the Reference Range

Many factors influence the reference range. Reference ranges may differ between labs depending on analytical technique, reagent, and equipment. The initial assumption that the sample

population is normal may be false. For example, the reference range is inaccurate if too many individuals with covert disease (i.e., no signs or symptoms of disease) are included in the sample population. Failure to control for physiologic variables (e.g., age, gender, ethnicity, body mass, diet, posture, and time of day) introduces many unrelated factors and may result in an inaccurate reference range. Reference ranges calculated from nonrandomly distributed (non-Gaussian) test results or from a small number of samples may not be accurate.

Reference ranges may change as new information relating to disease and treatments becomes available. For example, the National Cholesterol Education Program's 2002 Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) lowered and more closely spaced reference range cutoff points for low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TGs) and recommended dose-adjusted drug therapy to achieve specific cholesterol goals.[4] Based on newer evidence, the 2013 American College of Cardiology/American Heart Association Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults does not recommend specific LDL-C treatment targets.[5] The generally accepted upper limit of normal (ULN) for thyroid-stimulating hormone (TSH) (4.12 mIU/L) is based on data from the National Health and Nutrition Examination Survey.[6] But the availability of more sensitive assays and the recognition that the original reference population data were skewed has led some clinicians to conclude that the ULN for TSH should be lowered.[7]

Critical Value

The term *critical value* refers to a result that is far enough outside the reference range that it indicates impending morbidity (e.g., potassium <2.8 mEq/L). Because laboratory personnel are not in a position to consider mitigating circumstances, a responsible member of the healthcare team is notified immediately on discovery of a critical value test result. Critical values may not always be clinically relevant because the reference range varies for the reasons discussed above.

Semiquantitative Tests

A *semiquantitative test* is a test whose results are reported as either negative or with varying degrees of positivity but without exact quantification. For example, urine glucose and urine ketones are reported as negative or 1+, 2+, 3+; the higher numbers represent a greater amount of the measured substance in the urine but not a specific concentration.

Sensitivity

The *sensitivity* of a test refers to the ability of the test to identify positive results in patients who actually have the disease (TP rate).[8,9] Sensitivity assesses the proportion of TPs disclosed by the test (**Table 1-2**). A test is completely sensitive (100% sensitivity) if it is positive in every patient who actually has the disease. The higher the test sensitivity, the lower the chance of a false-negative result; the lower the test sensitivity, the higher the chance of a false-negative result. However, a highly sensitive test is not necessarily a highly specific test (see below).

TABLE 1-2. Calculation of Sensitivity and Specificity[a]

SCREENING TEST RESULT	DISEASED	NOT DISEASED	TOTAL
Positive	TP	FP	TP + FP
Negative	FN	TN	FN + TN
Total	TP + FN	FP + TN	TP + FP + FN + TN

FN = diseased persons not detected by test (false negatives); FP = nondiseased persons positive to test (false positives); TN = nondiseased persons negative to test (true negatives); TP = diseased persons detected by test (true positives).
[a]Sensitivity = [TP ÷ (TP + FN)] x 100%. Specificity = [TN ÷ (TN + FP)] x 100%.

Highly sensitive tests are preferred when the consequences of not identifying the disease are serious; less sensitive tests may be acceptable if the consequence of an FN is less significant or if low sensitivity tests are combined with other tests. For example, inherited phenylalanine hydroxylase deficiency (phenylketonuria [PKU]) results in increased phenylalanine concentrations. High phenylalanine concentrations damage the central nervous system and are associated with mental retardation. Mental retardation is preventable if PKU is diagnosed and dietary interventions initiated before 30 days of age. The phenylalanine blood screening test, used to screen newborns for PKU, is a highly sensitive test when testing infants at least 24 hours of age.[10] In contrast, the prostate-specific antigen (PSA) test, a test commonly used to screen men for prostate cancer, is highly specific but has low sensitivity, especially at low PSA cutoff values of 4–10 ng/mL.[11] Thus, PSA cannot be relied on as the sole prostate cancer screening method.

Sensitivity also refers to the range over which a quantitative assay can accurately measure the analyte. In this context, a sensitive test is one that can measure low levels of the substance; an insensitive test cannot measure low levels of the substance accurately. For example, a digoxin assay with low sensitivity might measure digoxin concentrations as low as 0.7 ng/mL. Concentrations below 0.7 ng/mL would not be measurable and would be reported as <0.7 ng/mL whether the digoxin concentration was 0.69 ng/mL or 0.1 ng/mL. Therefore, this relatively insensitive digoxin assay would not differentiate between medication nonadherence with an expected digoxin concentration of 0 ng/mL and low concentrations associated with inadequate dosage regimens.

Specificity

Specificity refers to the percent of negative results in people without the disease (TN rate).[8,9] Specificity assesses the proportion of TNs disclosed by the test (Table 1-2); the lower the specificity, the higher the chance of a false-positive result. A test with a specificity of 95% for the disease in question indicates

that the disease will be detected in 5% of people without the disease. Tests with high specificity are best for confirming a diagnosis because the tests are rarely positive in the absence of the disease. Several newborn screening tests (e.g., PKU, galactosemia, biotinidase deficiency, congenital hypothyroidism, and congenital adrenal hyperplasia) have specificity levels above 99%.[12] In contrast, the erythrocyte sedimentation rate (ESR) is a nonspecific test; infection, inflammation, and plasma cell dyscrasias increase the ESR.

Specificity as applied to quantitative laboratory tests refers to the degree of cross-reactivity of the analyte with other substances in the sample. Quinine may cross react with or be measured as quinidine in some assays, falsely elevating reported quinidine concentrations. Phenazopyridine interferes with urine ketone tests using sodium nitroprusside (e.g., Ketostix).

Specimen

A *specimen* is a sample (e.g., whole blood, plasma, serum, urine, stool, sputum, sweat, gastric secretions, exhaled air, cerebrospinal fluid, or tissues) that is used for laboratory analysis. Plasma is the watery acellular portion of blood. Plasma contains dissolved proteins (e.g., albumin, globulins, fibrinogen, enzymes, and hormones), electrolytes (e.g., sodium, potassium, chloride, calcium, and magnesium), lipids, carbohydrates, amino acids, and other organic substances (e.g., urea, uric acid, creatinine, bilirubin, ammonium ions). Serum is the liquid that remains after the fibrin clot is removed from plasma. Although some laboratory tests are performed only on plasma (e.g., prothrombin time, activated partial thromboplastin time [aPTT], D-dimer, and fibrinogen concentrations) or serum (e.g., albumin, creatinine, bilirubin, and acetaminophen concentrations), other laboratory tests can be performed on either plasma or serum (e.g., glucose, cortisol, electrolytes, and phenytoin concentrations). Some tests are performed on whole blood (e.g., blood gases, hemoglobin, hematocrit, complete blood count [CBC], and ESR).

LABORATORY TEST RESULTS

Units Used in Reporting Laboratory Results

Laboratory test results are reported with a variety of units. For example, four different units are used to report serum magnesium concentration (1 mEq/L = 1.22 mg/dL = 0.5 mmol/L = 12.2 mg/L). Additionally, the same units may be reported in different ways. For example, mg/dL, mg/100 mL, and mg% are equivalent units. Enzyme activity is usually reported in terms of units, but the magnitude varies widely and depends on the methodology. Rates are usually reported in volume per unit of time (e.g., CrCl is measured in mL/min or L/hr), but the ESR is reported in mm/hr and coagulation test results are reported in seconds or minutes. This lack of standardization is confusing and may lead to misinterpretation of the test results.

The International System of Units (Système Internationale d'Unités, or SI) was created about 50 years ago to standardize quantitative units worldwide.[13] Four base units and symbols are designated: length (meter, m), mass (kilogram, kg), time (second, s), and substance (mole, mol). Five derived units are designated: volume (liter, L, 10^{-3} m^3), force (newton, N, kg ms^{-2}), pressure (pascal, Pa, kg m^{-1} s^{-2}), energy (joule, J, kg m^2 s^{-2}), and power (watt, W, kg m^2 s^{-3}). However, it is difficult for clinicians to relate to molar concentrations (e.g., serum cholesterol 4.14 mmol × L^{-1} versus 160 mg/dL, or HbA1c mmol/mL versus 8%). In the United States, most laboratory results are reported in conventional units.

Rationale for Ordering Laboratory Tests

Laboratory tests are performed with the expectation that the results will

- discover occult disease
- confirm a suspected diagnosis
- differentiate among possible diagnoses
- determine the stage, activity, or severity of disease
- detect disease recurrence
- assess the effectiveness of therapy
- guide the course of therapy

Laboratory tests are categorized as screening or diagnostic tests. Screening tests, performed in individuals without signs or symptoms of disease, detect disease early when interventions (e.g., lifestyle modifications, drug therapy, and surgery) are likely to be effective. Screening tests are performed on healthy individuals and are generally inexpensive, quick and easy to perform, and reliable, although they do not provide a definitive answer. Screening tests require confirmation with other clinical tests. Diagnostic tests are performed on at-risk individuals, are typically more expensive, and are associated with some degree of risk but provide a definitive answer.[14]

Comparative features of screening tests are listed in **Table 1-3**. Examples of screening tests include the Papanicolaou smear, lipid profile, PSA, fecal occult blood, tuberculin skin test, sickle cell tests, blood coagulation tests, and serum chemistries. Screening tests may be performed on healthy outpatients (e.g., ordered by the patient's primary care provider or performed during public health fairs) or on admission to an acute care facility (e.g., prior to scheduled surgery). Abnormalities identified during screening are followed by more specific tests to confirm the results.

TABLE 1-3. Comparative Features of Screening and Diagnostic Laboratory Tests

FEATURE	SCREENING TEST	DIAGNOSTIC TEST
Simplicity of test	Fairly simple	More complex
Target population	Individuals without signs or symptoms of the disease	Individuals with signs or symptoms of the disease
Characteristic	High sensitivity	High specificity
Disease prevalence	Relatively common	Common or rare
Risks	Acceptable to population	Acceptable to individual

Source: Reference 15.

Screening tests must be cost-effective and population-appropriate. The number needed to screen is defined as "the number of people that need to be screened for a given duration to prevent one death or one adverse event."[16] For example, 84 women between the ages of 40 and 84 years need to undergo annual mammographic screening to prevent one death from breast cancer.[17]

Diagnostic tests are performed in individuals with signs or symptoms of disease, a history suggestive of a specific disease or disorder, or an abnormal screening test. Diagnostic tests are used to confirm a suspected diagnosis, differentiate among possible diagnoses, determine the stage of activity of disease, detect disease recurrence, and assess and guide the therapeutic course. Diagnostic test features are listed in Table 1-3. Examples of diagnostic tests include blood cultures, serum cardiac-specific troponin I and T, kidney biopsy, and the cosyntropin test.

Many laboratories group a series of related tests (screening and/or diagnostic) into a set called a *profile*. For example, the basic metabolic panel (BMP) includes common serum electrolytes (sodium, potassium, and chloride), carbon dioxide content, blood urea nitrogen (BUN), calcium, creatinine, and glucose. The comprehensive metabolic panel includes the BMP plus albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and total protein. Grouped together for convenience, some profiles may be less costly to perform than the sum of the cost of each individual test. However, profiles may generate unnecessary patient data. Attention to cost is especially important in the current cost-conscious era. A test should not be done if it is unnecessary, redundant, or provides suboptimal clinical data (e.g., non-steady-state serum drug concentrations). Before ordering a test, the clinician should consider the following questions:

- Was the test recently performed and in all probability the results have not changed at this time?
- Were other tests performed that provide the same information?
- Can the information be estimated with adequate reliability from existing data?
  (For example, CrCl can be estimated using age, height, weight, and SCr rather than measured from a 24-hour urine collection. Serum osmolality can be calculated from electrolytes and glucose rather than measured directly.)
- What will I do if results are positive or negative (or absent or normal)? (For example, if the test result will not aid in clinical decisions or change the diagnosis, prognosis, or treatment course, the benefits from the test are not worth the cost of the test.)

Factors That Influence Laboratory Test Results

Laboratory results may be inconsistent with patient signs, symptoms, or clinical status. Before accepting reported laboratory values, clinicians should consider the numerous laboratory-specific and patient-specific factors that may influence the results (**Table 1-4**). For most of the major tests discussed in this book, a Quickview chart summarizes information helpful in interpreting results. **Figure 1-2** depicts the format and content of a typical Quickview chart.

TABLE 1-4. Factors That Influence Assessment of Laboratory Results

Assay used and form of analyte
Free form
Bound form
Clinical situation
Acuity of disease
Severity of disease
Demographics
Age
Gender
Ethnicity
Height
Weight
Body surface area
Drugs
Drug–drug interactions
Drug–assay interactions
Food
Time of last meal
Type of food ingested
Nutritional status
Well nourished
Poorly nourished
Posture
Upright
Supine
Pregnancy
Specimen analyzed
Serum
Plasma
Whole blood (venous or arterial)
Cerebrospinal fluid
Urine
Stool
Sputum
Other (e.g., tissue, sweat, gastric contents, effusions)
Temporal relationships
Time of day
Time of last dose

QUICKVIEW | Contents of a Typical Quickview Chart

PARAMETER	DESCRIPTION	COMMENTS
Common reference ranges		
Adults	Reference range in adults	Variability and factors affecting range
Pediatrics	Reference range in children	Variability, factors affecting range, age grouping
Critical value	Value beyond which immediate action usually needs to be taken	Disease-dependent factors; relative to reference range; value is a multiple of upper normal limit
Inherent activity	Does substance have any physiological activity?	Description of activity and factors affecting activity
Location		
Production	Is substance produced? If so, where?	Factors affecting production
Storage	Is substance stored? If so, where?	Factors affecting storage
Secretion/excretion	Is substance secreted/excreted? If so, where/how?	Factors affecting secretion or excretion
Causes of abnormal values		
High	Major causes	Modification of circumstances, other related causes or drugs that are commonly monitored with this test
Low	Major causes	
Signs and symptoms		
High level	Major signs and symptoms with a high or positive result	Modification of circumstances/other related signs and symptoms
Low level	Major signs and symptoms with a low result	Modification of circumstances/other related causes
After event, time to....		
Initial elevation	Minutes, hours, days, weeks	Assumes acute insult
Peak values	Minutes, hours, days, weeks	Assumes insult not yet removed
Normalization	Minutes, hours, days, weeks	Assumes insult removed and nonpermanent damage
Causes of spurious results	List of common causes	Modification of circumstances/assay specific
Additional information	Any other pertinent information regarding the laboratory value or assay	

FIGURE 1-2. Contents of a typical Quickview chart.

Laboratory-Specific Factors

Laboratory errors are uncommon but may occur. Defined as a test result that is not the true result, *laboratory error* most appropriately refers to inaccurate results that occur because of an error made by laboratory personnel or equipment. However, laboratory error is sometimes used to refer to otherwise accurate results rendered inaccurate by specimen-related issues. Laboratory errors should be suspected for one or more of the following situations:

- The result is inconsistent with trend in serial test results.
- The magnitude of error is great.
- The result is not in agreement with a confirmatory test result.
- The result is inconsistent with clinical signs or symptoms or other patient-specific information.

True laboratory errors (inaccurate results) are caused by one or more laboratory processing or equipment errors, such as deteriorated reagents, calibration errors, calculation errors, misreading the results, computer entry or other documentation errors, or improper sample preparation. For example, incorrect entry of thromboplastin activity (ISI [international sensitivity index]) when calculating the international normalized ratio (INR) results in accurately assayed but incorrectly reported INR results.

Accurate results may be rendered inaccurate by one or more specimen-related problems. Improper specimen handling prior to or during transport to the laboratory may alter analyte concentrations between the time the sample was obtained from the patient and the time the sample was analyzed in the laboratory.[18] For example, arterial blood withdrawn for blood gas analysis must be transported on ice to prevent continued in vitro changes in pH, $PaCO_2$, and PaO_2. Failure to remove the plasma or serum from the clot within four hours of obtaining blood for serum potassium analysis may elevate the reported serum potassium concentration. Red blood cell hemolysis

elevates the serum potassium and phosphate concentrations. Failure to refrigerate samples may cause falsely low concentrations of serum enzymes (e.g., CK). Prolonged tourniquet time may hemoconcentrate analytes, especially those that are highly protein bound (e.g., calcium).

Patient-Specific Factors

Laboratory test values cannot be interpreted in isolation of the patient. Numerous age-related (e.g., decreased renal function) and other patient-specific factors (e.g., time of day, posture) as well as disease-specific factors (e.g., time course) affect laboratory results. The astute clinician assesses laboratory data in context of all that is known about the patient.

Time course. Incorrectly timed laboratory tests produce misleading laboratory results. Disease states, normal physiologic patterns, pharmacodynamics, and pharmacokinetics time courses must be considered when interpreting laboratory values. For example, digoxin has a prolonged distribution phase. Digoxin serum concentrations obtained before tissue distribution is complete do not accurately reflect true tissue drug concentrations. Postmyocardial infarction enzyme patterns are complex and evolve over a prolonged period of time. For example, CK increases about six hours following myocardial infarction (MI) and returns to baseline about 48–72 hours after the MI. Following MI, LDH increases about 12–24 hours following MI and returns to baseline about 10 days after the MI. Troponin increases a few hours following MI and returns to baseline in about five to seven days. Serial samples are used to assess myocardial damage.

Laboratory samples obtained too early or too late may miss critical changes and lead to incorrect assessments. For example, cosyntropin (synthetic adrenocorticotropic hormone [ACTH]) tests adrenal gland responsiveness. The baseline 8 a.m. plasma cortisol is compared to the stimulated plasma cortisol obtained 30 and 60 minutes following injection of the drug. Incorrect timing leads to incorrect results. The sputum acid-fast bacilli (AFB) smear may become AFB-negative with just a few doses of antituberculous drugs, but the sputum culture may remain positive for several weeks. Expectations of a negative sputum culture too early in the time course may lead to the inappropriate addition of unnecessary antituberculous drugs.

Non-steady-state drug concentrations are difficult to interpret; inappropriate dosage adjustments (usually inappropriate dosage increases) may occur if the clinician fails to recognize that a drug has not reached steady-state concentrations. Although non-steady-state drug concentrations may be useful when assessing possible drug toxicity (e.g., overdose situations and new onset adverse drug events), all results need to be interpreted in the context of the drug's pharmacokinetics. Absorption, distribution, and elimination may change with changing physiology. For example, increased/decreased hepatic or renal perfusion may affect the clearance of a drug. Some drugs (e.g., phenytoin) have very long half-lives; constantly changing hemodynamics during an acute care hospitalization may prevent the drug from achieving steady state while the patient is acutely ill.

Age. Age influences many physiologic systems. Age-related changes are well-described for neonates and young children, but less data are available for the elderly and the very elderly (usually described as ≥90 years of age). Age influences some but not all laboratory values; not all changes are clinically significant.

Pediatric reference ranges often reflect physiologic immaturity, with laboratory values approaching those of healthy adults with increasing age. For example, the CBC (hemoglobin, hematocrit, RBC count, and RBC indices) ranges are greatly dependent on age with different values reported for premature neonates, term neonates, and young children. The fasting blood glucose reference range in premature neonates is approximately 20–65 mg/dL compared to 60–105 mg/dL for children two years of age and older and 70–110 mg/dL for adults. The SCr reference range for children 1–5 years of age differs from the reference range for children 5–10 years of age (0.3–0.5 mg/dL versus 0.5–0.8 mg/dL). Reference ranges for children are well-described because it is relatively easy to identify age-differentiated populations of healthy children. Most laboratory reference texts provide age-specific reference values.

Geriatric reference ranges are more difficult to establish because of physiologic variability with increasing age and the presence of symptomatic and asymptomatic disease states that influence reference values. Diet (e.g., malnutrition) also influences some laboratory results. Some physiologic functions (e.g., cardiac, pulmonary, renal and metabolic functions) progressively decline with age, but each organ declines at a different rate.[19] Other physiologic changes associated with aging include decreased body weight, decreased height, decreased total body water, increased extracellular water, increased fat percentage, and decreased lean tissue percentage; and loss of cell membranes integrity.[19] Published studies sometimes lead to contradictory conclusions due to differences in study methodology (e.g., single point versus longitudinal evaluations) and populations assessed (e.g., nursing home residents versus general population). Limited data are available for the very elderly (≥90 years of age).[20] Most laboratory reference texts provide age-specific reference values.

Despite the paucity of data and difficulties imposed by different study designs and study populations, there is general consensus that some laboratory reference ranges are unchanged, some are different but of uncertain clinical significance, and some are significantly different in the elderly (**Table 1-5**). For example, decreased lean muscle mass with increased age results in decreased creatinine production. Decreased renal function is associated with decreased creatinine elimination. Taken together, the SCr reference range in the elderly is not different from younger populations; however, CrCl clearly declines with age.

Significant age-related changes are reported for the two-hour postprandial glucose test, serum lipids, and arterial oxygen pressure (Table 1-5). The two-hour postprandial glucose increases by about 5–10 mg/dL per decade. Progressive ventilation-perfusion mismatching from loss of elastic recoil with increasing age causes progressively decreased arterial

TABLE 1-5. Laboratory Testing: Tests Affected by Aging

No change
Amylase
Lipase
Hemoglobin
Hematocrit
RBC count
RBC indices
Platelet count
WBC count and differential
Serum electrolytes (sodium, potassium, chloride, bicarbonate, magnesium)
Coagulation
Total iron-binding capacity
Thyroid function tests (thyroxine, T_3RU)
Liver function tests (AST, ALT, LDH)
Some change (unclear clinical significance)
Alkaline phosphatase
ESR
Serum albumin
Serum calcium
Serum uric acid
Thyroid function tests (TSH, T_3)
Clinically significant change
Arterial oxygen pressure
Two-hour postprandial glucose
Serum lipids (total cholesterol, LDL, TGs)
Serum testosterone (in men)
Serum estradiol (in women)
No change but clinically significant decrease in renal function
SCr

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ESR = erythrocyte sedimentation rate; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; TSH = thyroid-stimulating hormone; T_3 = triiodothyronine; T_3RU = triiodothyronine resin uptake; RBC = red blood cell; SCR = serum creatinine; TGs = triglycerides; WBC = white blood cell.
Source: References 19–27.

oxygen pressure with increasing age. Total cholesterol and LDL-C increase with age then decline in the very old.

Genetics, ethnicity, and gender. Inherited ethnic and/or gender differences are identified for some laboratory tests. For example, the hereditary anemias (e.g., thalassemias and sickling disorders such as sickle cell anemia) are more common in individuals with sub-Saharan African, Asian, Middle Eastern, and Mediterranean, ancestry.[28] Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an example of an inherited sex-linked (X chromosome) enzyme deficiency found primarily in men of African, Asian, Middle Eastern, and Mediterranean ancestry.[29] The A-G6PD variant occurs mostly in Africans and affects about 13% of African-American males and 3% of African-American females in the United States. The Mediterranean G6PD variant, associated with a less common but more severe enzyme deficiency state, occurs mostly in individuals of Greek, Sardinian, Kurdish, Asian, and Sephardic Jewish ancestry.

Other enzyme polymorphisms influence drug metabolism. The genetically-linked absence of an enzyme may lead to drug toxicity secondary to drug accumulation or lack of drug effectiveness if the parent compound is an inactive prodrug (e.g., codeine). The cytochrome P450 (CYP450) superfamily consists of greater than 100 isoenzymes with selective but overlapping substrate specificity. Some individuals are poor metabolizers, while some are hyperextensive metabolizers. Several of the cytochrome P450 phenotypes vary by race. For example, the CYP2D6 poor metabolism phenotype occurs in 5–10% of Caucasians, and the CYP2C19 poor metabolism phenotype occurs in 10–30% of Asians.[30,31]

Additional enzyme polymorphisms include pseudocholinesterase deficiency, phenytoin hydroxylation deficiency, inefficient N-acetyltransferase activity, inefficient or rapid debrisoquine hydroxylase activity, diminished thiopurine methyltransferase activity, partial dihydropyrimidine dehydrogenase inactivity, and defective uridine diphosphate glucuronosyltransferase activity.[32] Other examples of genetic polymorphisms include variations in the β-2 adrenoceptor gene that influence response to sympathomimetic amines and variations in drug transporters such as P-glycoprotein, multidrug resistance-associated proteins (e.g., MRP1, MRP2, MRP3), and organic anion-transporting polypeptides (e.g., OATP1, OATP2).[32]

Biologic rhythms. Biologic rhythms are characterized as short (<30 minutes), intermediate (greater than 30 minutes but less than six days), and long (greater than six days).[33] The master clock, located in the suprachiasmatic nucleus of the hypothalamus, coordinates timing signals and multiple peripheral clocks.[34] A circadian rhythm is a 24-hour, endogenously generated cycle.[35] Well-described, human circadian rhythms include body temperature, cortisol production, melatonin production, and hormonal production (gonadotropin, testosterone, growth hormone, and thyrotropin). Platelet function, cardiac function, and cognition also follow a circadian rhythm.[36]

Other laboratory parameters follow circadian patterns. For example, statistically significant circadian rhythms have been reported for CK, ALT, γ-glutamyl transferase, LDH, and some serum lipids.[37,38] Glomerular filtration has a circadian rhythm.[39] Circadian variations in aminoglycoside pharmacokinetics, including netilmicin, amikacin, and gentamicin, have been reported.[40] Although the clinical significance of diurnally variable laboratory results is not well understood, diurnal variability should be considered when assessing laboratory values. Obtaining laboratory results at the same time of day (e.g., routine 7 a.m. blood draws) minimizes variability due to circadian rhythms. Different results obtained at different times of the day may be due to circadian variability rather than acute physiologic changes.

Other well-described biologic rhythms include the eight-hour rhythm for circulating endothelin, the approximately weekly (circaseptan) rhythm for urinary 17-ketosteroid excretion, the monthly rhythms of follicle-stimulating hormone [FSH], luteinizing hormone, progesterone production, and the seasonal rhythms for cholesterol and 25-hydroxycholecalciferol.[41,42]

Drugs. The four generally accepted categories of drug–laboratory interactions include methodological interference; drug-induced, end-organ damage; direct pharmacologic effect; and a miscellaneous category. Many drugs interfere with analytical methodology. Drugs that discolor the urine interfere with fluorometric, colorimetric, and photometric tests and mask abnormal urine colors. For example, amitriptyline turns the urine a blue-green color and phenazopyridine and rifampin turn the urine an orange-red color. Other drugs directly interfere with the laboratory assay. For example, high doses of ascorbic acid (>500 mg/day) cause false-negative stool occult blood tests. Some drugs interfere with urinary fluorescence tests for urine catecholamines by producing urinary fluorescence themselves (e.g., ampicillin, chloral hydrate, and erythromycin).

Direct drug-induced, end-organ damage (e.g., kidney, liver, and bone marrow) change the expected laboratory results. For example, amphotericin B causes renal damage evidenced by increased SCr. Bone marrow suppressants, such as doxorubicin and bleomycin, cause thrombocytopenia. Some drugs alter laboratory results as a consequence of a direct pharmacologic effect. Thiazide and loop diuretics increase serum uric acid by decreasing uric acid renal clearance or tubular secretion. Narcotics, such as codeine and morphine sulfate, increase serum lipase by inducing spasms of the sphincter of Oddi. Urinary specific gravity is increased in the presence of dextran. Other examples of drug–laboratory interactions include drugs that cause a positive direct Coombs test (e.g., isoniazid, sulfonamides, and quinidine), drugs that cause a positive antinuclear antibody test (e.g., penicillins, sulfonamides, and tetracyclines), and drugs that inhibit bacterial growth in blood or urine cultures (e.g., antibiotics).

Thyroid function tests are a good example of the complexity of potential drug-induced laboratory test changes. Thyroxine (T_4) and triiodothyronine (T_3) are displaced from binding proteins by salicylates, heparin, and high doses of furosemide. Free T_4 levels initially increase, but chronic drug administration results in decreased T_4 levels with normal TSH levels. Phenytoin, phenobarbital, rifampin, and carbamazepine stimulate hepatic metabolism of thyroid hormone, resulting in decreased serum hormone concentration. Amiodarone, high-dose β-adrenergic blocking drugs, glucocorticosteroids, and some iodine contrast dyes interfere with the conversion of T_4 to T_3. Ferrous sulfate, aluminum hydroxide, sucralfate, colestipol, and cholestyramine decrease T_4 absorption. Somatostatin, octreotide, and glucocorticosteroids suppress TSH production.

Pregnancy. Pregnancy is a normal physiologic condition that alters the reference range for many laboratory tests. Normal pregnancy increases serum hormone concentrations (e.g., estrogen, testosterone, progesterone, human chorionic gonadotropin, prolactin, corticotropin-releasing hormone, ACTH, cortisol, and atrial natriuretic hormone). The plasma volume increases by 30–50%, resulting in a relative hyponatremia (e.g., serum sodium decreased by about 5 mEq/L) and modest decreases in hematocrit. The metabolic adaptations to pregnancy include increased RBC mass and altered carbohydrate (e.g., 10–20% decrease in fasting blood glucose) and lipid (e.g., 300% increase in TGs and a 50% increase in total cholesterol) metabolism. Pregnancy changes the production and elimination of thyroid hormones, resulting in different reference values over the course of pregnancy.[43] For example, T_4-binding globulin increases during the first trimester, but pregnancy-associated accelerated thyroid hormone metabolism occurs later in the pregnancy. Other physiologic changes during pregnancy include an increased cardiac output (increases by 30–50%), decreased systemic vascular resistance, increased glomerular filtration rate (increases by 40–50%), shortened prothrombin and partial thromboplastin times, and hyperventilation resulting in compensated respiratory alkalosis and increased arterial oxygenation.[44]

Other Factors

Organ function, diet, fluid status, patient posture, and altitude also affect some laboratory tests.

Organ function. Renal dysfunction may lead to hyperkalemia, decreased CrCl, and hyperphosphatemia. Hepatic dysfunction may lead to reduced clotting factor production with prolonged partial thromboplastin times and prothrombin times. Bone marrow dysfunction may lead to pancytopenia.

Diet. Serum glucose and lipid profiles are best assessed in the fasting state. Unprocessed grapefruit juice down-regulates intestinal CYP3A4 and increases the bioavailability of some orally administered drugs.

Fluid status. Dehydration is associated with a decreased amount of fluid in the bloodstream; all blood constituents (e.g., sodium, potassium, creatinine, glucose, and BUN) become more concentrated. This effect is called *hemoconcentration.* Although the absolute amount of the substance in the body has not changed, the loss of fluid results in an abnormally high concentration of the measured analyte. The converse is true with hemodilution. Relativity must be applied or false impressions may arise (**Minicase 2**).

Posture. Plasma renin release is stimulated by upright posture, diuretics, and low-sodium diets; plasma renin testing usually occurs after two to four weeks of normal sodium diets under fasting supine conditions.

Altitude. At high altitude, hemoglobin initially increases secondary to dehydration. However, hypoxia stimulates erythropoietin production, which in turn stimulates hemoglobin production resulting in increased hemoglobin concentration and increased blood viscosity. Serum hemoglobin reference ranges are adjusted progressively upward for individuals living above 1000 feet.[45]

MINICASE 2

Interpretation of Laboratory Parameters in Dehydration

Jenny M., a 27-year-old female, was lost in the woods for several days without food or water. It was warm when the sun was out but cool at night. When rescued, she was happy to be found but was confused and weak. She had multiple scratches on her arms and legs and a deep gash across her cheek. Jenny M. was not taking any prescription or nonprescription medications.

On arrival in the emergency department, Jenny M. is weak, lethargic, and confused. Pertinent findings on physical examination include hypotension, tachycardia, tachypnea, and decreased skin turgor. Her mouth and lips are very dry. A BMP and CBC is ordered. The BMP was notable for elevated serum electrolytes, BUN, and SCr. The BUN-to-creatinine ratio is >20 to 1. The CBC is notable for an elevated white blood cell count with an increased percentage of bands and elevated platelets, hematocrit, and hemoglobin. Fluid resuscitation and antibiotics are ordered.

QUESTION: The prescribed antibiotic is dosed according to renal function. The manufacturer provides dosing recommendations based on estimated CrCl using the Cockcroft Gault equation. Is it appropriate to use this patient's admission creatinine to estimate her CrCl?

DISCUSSION: No. This patient is severely dehydrated; all laboratory parameters are hemoconcentrated. Her admission SCr is high and underestimates her renal function; however, it is possible that the severe dehydration damaged her kidneys. The best approach is to give one dose of the antibiotic and then monitor her renal function closely over the next 24–48 hours, redosing the antibiotic as indicated.

NONCENTRALIZED LABORATORY TESTS

Point-of-Care Testing

Point-of-care testing (POCT), also known as *near patient testing*, *bedside testing*, or *extra-laboratory testing*, is clinician-directed diagnostic testing performed at or near the site of patient care rather than in a centralized laboratory.[46,47] The POCT equipment ranges from small, hand-held devices to table-top analyzers. In vitro, in vivo, and ex vivo POCT refer to tests performed near the patient (e.g., fingerstick blood glucose), in the patient (e.g., specialized intra-arterial catheter that measures lactate), and just outside the patient (e.g., intra-arterial catheter attached to an external analyzer). Although POCT is not a new concept, recent technological advances (e.g., microcomputerization, miniaturization, biosensor development, etc.) have rapidly expanded the variety of available POCT beyond the traditional urinalysis dipsticks or fingerstick blood glucose monitors (**Table 1-6**).

TABLE 1-6. Common Point-of-Care Tests

Urine pregnancy test
Urine leukocytes or nitrite
Blood glucose
INR
Hemoglobin
Fecal occult blood
Throat swab for group A streptococci
C-reactive protein
Quantitative β-human chorionic gonadotropin
HbA1c
Nose/throat swab for influenza
Platelet count

HbA1c = glycated hemoglobin; INR = international normalized ratio.
Source: Reference 48.

The major advantages of POCT include reduced turnaround time and test portability. Reduced turnaround time is especially advantageous in settings where rapidly available laboratory test results may improve patient care (e.g., emergency departments, operating rooms, critical care units, accident scenes, and patient transport). Reduced turnaround time also enhances patient care in more traditional ambulatory settings by reducing patient and provider time and minimizing delays in initiating therapeutic interventions. Patient care sites without local access to centralized laboratories (e.g., nursing homes, rural physician practices, and military field operations) also benefit from POCT. Other POCT advantages include blood conservation (POCT usually require drops of blood as opposed to the several milliliters required for traditional testing); less chance of preanalytical error from inappropriate transport, storage, or labeling of samples; and overall cost savings. Although the per test cost is usually higher with POCT, cost analyses must consider the per unit cost of the test as well as other costs such as personnel time, length of stay, and quality of life.

The major disadvantages of POCT include misuse or misinterpretation of results, loss of centrally-generated epidemiological data, documentation errors, inappropriate test material disposal, and quality assurance issues. All laboratory testing must meet the minimum standards established by the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88).[49] Under CLIA-88, tests are categorized into one of three groups based on potential public health risk: waived tests, tests of moderate complexity, and tests of high complexity. Waived tests (e.g., fecal occult blood test) pose no risk of harm to the patient if used incorrectly or use such simple and accurate methodologies that inaccurate results are unlikely. Many POCT meet the criteria for waived status but increasingly sophisticated POCT

TABLE 1-7. Types of Nonprescription In Vitro Diagnostic Tests

TEST	BODY FLUID OR SPECIMEN TESTED
Alcohol	Breath
Blood, fecal occult	Feces
Drugs of abuse (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine metabolites, methadone, methylenedioxymethamphetamine, morphine, phencyclidine)	Urine, hair
Fertility, male	Semen
FSH (menopausal)	Urine
Glucose	Blood, urine
HDL cholesterol	Blood
Hemoglobin	Blood
HbA1c	Blood
HIV-1	Blood
Human chorionic gonadotropin (pregnancy)	Urine, serum
Ketones	Blood, urine
Luteinizing hormone (ovulation)	Urine
Thyroid-stimulating hormone	Blood
Triglycerides	Blood

FSH = follicle-stimulating hormone; HbA1c = glycated hemoglobin; HDL = high-density lipoprotein; HIV-1 = human immunodeficiency virus type 1.

may be subject to more stringent control. State-specific regulations may be more stringent than federal regulations.

Home Testing

Home testing refers to patient-directed diagnostic and monitoring testing usually performed by the patient or family member at home. More than 500 Food and Drug Administration (FDA)-approved, home-use, nonprescription laboratory test kits are marketed; home glucose and pregnancy testing are among the most popular (**Table 1-7**). Many non-FDA-approved home-testing kits are marketed via the Internet. The FDA's Office of In Vitro Diagnostics and Radiological Health maintains a searchable list of approved home-testing kits (http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/LabTest/ucm126079.htm). Advantages of home testing include convenience, cost savings (as compared to physician office visit), quickly available results, and privacy. Home monitoring of chronic drug therapy, such as blood glucose control with insulin therapy, may give the patient a better sense of control over the disease and improve patient outcomes. Disadvantages of home testing include misinterpretation of test results, delays in seeking medical advice, and lack of pretest and posttest counseling and psychological support. In addition, home test kits typically do not provide the consumer with information regarding sensitivity, specificity, precision, or accuracy. Home-use test kits are marketed as either complete test kits (consumers obtain their own sample, test the sample, and read the results) or as collection kits (consumers obtain the sample, mail the sample to the laboratory, and receive the results by mail or telephone). As always, consumers should read and follow the test instructions to minimize testing error.

GUIDELINES FOR INTERPRETING LABORATORY RESULTS

Laboratory results must be interpreted in context of the patient and the limitations of the laboratory test. However, a laboratory result is only one piece of information; diagnostic and therapeutic decisions cannot be made on the basis of one piece of information. Clinicians typically give more weight to the presence or absence of signs and symptoms associated with the medical problem rather than to an isolated laboratory report. For example, an asymptomatic patient with a serum potassium concentration of 3 mEq/L (reference range: 3.5–5 mEq/L) does not cause as much concern as a patient who has a concentration of 3.3 mEq/L but is symptomatic. Tests for occult disease, such as colon cancer, cervical cancer, and hyperlipidemia, are exceptions to this logic because the patients being tested are asymptomatic. Baseline results, rate of change, and patterns should be considered when interpreting laboratory results.

Baseline Results

Baseline studies establish relativity and are especially useful when reference ranges are wide or when reference values vary significantly among patients. For example, lovastatin and other hydroxymethylglutaryl coenzyme A reductase inhibitors cause myopathy and liver dysfunction in a small percentage of patients. The myopathy is symptomatic (muscle pain or weakness) and elevates CK concentrations. The drug-induced liver dysfunction is asymptomatic and causes elevated AST and ALT. Some clinicians establish a pretreatment baseline profile including CK, AST, and ALT and then conduct periodic testing thereafter to identify potential drug-induced toxicity. Creatine kinase has a wide reference range (55–170 units/L);

establishment of a baseline allows the clinician to identify early changes, even within the reference range. The baseline value is also used to establish relative therapeutic goals. For example, the aPTT is used to assess patient response to heparin anticoagulation. Therapeutic targets are expressed in terms of how much higher the patient's aPTT is compared to the baseline control.

Laboratory Value Compared to Reference Range

Not all laboratory values above the ULN require intervention. Risk-to-benefit considerations may require that some evidence of drug-induced organ damage is acceptable given the ultimate benefit of the drug. For example, a six-month course of combination drug therapy including isoniazid, a known hepatotoxin, is recommended for treatment of latent tuberculosis.[50] The potential benefit of at least six months of therapy (i.e., lifetime protection from tuberculosis in the absence of reinfection) means that clinicians are willing to accept some evidence of liver toxicity with continued drug therapy (e.g., isoniazid is continued until AST is greater than five times the ULN in asymptomatic individuals or greater than three times the ULN in symptomatic patients).[51]

Rate of Change

The *rate of change* of a laboratory value provides the clinician with a sense of risks associated with the particular signs and symptoms. For example, a patient whose RBC count falls from 5 million/mm^3 to 3.5 million/mm^3 over several hours is more likely to be symptomatic and need immediate therapeutic intervention than if the decline took place over several months.

Isolated Results Versus Trends

An isolated abnormal test result is difficult to interpret. However, one of several values in a series of results or similar results from the same test performed at two different times suggests a pattern or trend. For example, a random serum glucose concentration of 300 mg/dL (reference range ≤200 mg/dL in adults) might cause concern unless it was known that the patient was admitted to the hospital the previous night for treatment of diabetic ketoacidosis with a random serum glucose of 960 mg/dL. A series of laboratory values adds perspective to an interpretation but may increase overall costs.

Spurious Results

A *spurious laboratory value* is a false laboratory value. The only way to differentiate between an actual and a spurious laboratory value is to interpret the value in context of what else is known about the patient. For example, a serum potassium concentration of 5.5 mEq/L (reference range: 3.5–5 mEq/L) in the absence of significant electrocardiographic changes (i.e., wide, flat P waves, wide QRS complexes, and peaked T waves) and risk factors for hyperkalemia (i.e., renal insufficiency) is most likely a spurious value. Possible causes of falsely elevated potassium, such as hemolysis, acidosis, and laboratory error, have to be ruled out before accepting that the elevated potassium accurately reflects the patient's actual serum potassium. Repeat testing of suspected spurious laboratory values increases the cost of patient care but may be necessary to rule out an actual abnormality.

FUTURE TRENDS

As advances in miniaturization produce smaller and more portable analytical devices, POCT will progress and become more widely available. Real-time, in vivo POCT may become standard in many patient care areas. Laboratory test specificity and sensitivity will improve with more sophisticated testing. Genetic testing (laboratory analysis of human deoxyribonucleic acid [DNA], RNA, chromosomes, and proteins) will undergo rapid growth and development in the next few decades; genetic testing will be able to predict an individual's risk for disease, identify carriers of disease, establish diagnoses, and provide prognostic data. Genetic links for a diverse group of diseases including cystic fibrosis, Down syndrome, Huntington disease, breast cancer, Alzheimer disease, schizophrenia, PKU, and familial hypercholesterolemia are established; genetic links for many additional diseases will be established. Variations in DNA sequences will be well-described and linked to individualized, disease management strategies.[52] Developments in nanotechnology will provide simple and inexpensive in vitro and in vivo assessments. Advances in array-based technologies (i.e., simultaneous evaluation of multiple analytes from one sample) will reduce sample volume and cost.

PATIENT ASSESSMENT

Evaluation of patient laboratory data is an important component of designing, implementing, monitoring, evaluating, and modifying patient-specific medication therapy management plans. Depending on the setting, state laws, and collaborative practice agreements, some pharmacists have the authority to order and assess specific laboratory tests (e.g., drug serum concentrations, SCr, liver function tests, serum electrolytes) or to perform POCT (e.g., lipid screening profiles, prothrombin time, HbA1c, rapid strep test). Pharmacists in ambulatory clinics and acute care inpatient settings have routine access to the same patient laboratory data as all other members of the healthcare team, but many community-based pharmacists do not have access to patient laboratory data. Although lack of access to laboratory data is currently a barrier, the increasing use of electronic patient charts and databases will improve pharmacist access to patient laboratory data.

SUMMARY

Clinical laboratory tests are convenient methods to investigate disease-related and drug-related patient issues, especially because knowledge of pathophysiology and therapeutics alone is insufficient to provide high-quality clinical considerations. This chapter should help clinicians appreciate general causes

and mechanisms of abnormal test results. However, results within the reference range are not always associated with an absence of signs and symptoms. Many factors influence the reference range. Knowing the sensitivity, specificity, and predictive value is important in selecting an assay and interpreting its results. Additionally, an understanding of the definitions, concepts, and strategies discussed should also facilitate mastering information in the following chapters.

LEARNING POINTS

1. ***What factors should be considered when assessing a laboratory parameter that is outside the reference range?***

   ANSWER: The upper and lower limits of the reference range are not absolute; by definition, some normal results will fall outside the reference range. Other factors to consider include the sensitivity and specificity of the test, the critical value for the test, the acuity of the change, drug–drug and drug–test interactions, patient signs and symptoms, laboratory error, specimen handling, patient age, and timing of the test.

2. ***What factors should be considered when discussing PSA screening?***

   ANSWER: Sensitivity and specificity should be considered. Although PSA is specific for the prostate, it has a low sensitivity for detecting prostate cancer and is elevated by urethral instrumentation, prostatitis, urinary retention, prostatic needle biopsy, and benign prostatic hyperplasia. Specificity for prostate cancer is lower in older men with benign prostatic hyperplasia than in younger men without prostatic hyperplasia. Thus, an elevated PSA level found during screening may result in unnecessary biopsies, treatment, and complications. Many authorities do not recommend PSA-based screening for prostate cancer.[53]

3. ***What advantages and disadvantages should be considered when recommending at-home laboratory testing kits?***

   ANSWER: Advantages of patient-directed diagnostic and monitoring testing include convenience, cost savings as compared to a physician office visit, quickly available results, and privacy. Disadvantages include lack of information regarding sensitivity, specificity, precision, or accuracy; misinterpretation of the test results; the absence of pretest and posttest counseling; and delays in seeking medical advice. Patients who wish to purchase FDA-approved home-testing kits should be cautioned to seek advice before making treatment decisions based solely on home-testing laboratory results.

REFERENCES

1. Atkinson AJ, Colburn WA, DeGruttola VG et al. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther.* 2001; 69:89-95.
2. Gurol Y, Akan H, Izbirak G et al. The sensitivity and the specificity of rapid antigen test in streptococcal upper respiratory tract infections. *Int J Pediatr Otorhinolaryngol.* 2010; 74:591-93.
3. CLSI. Defining, establishing, and verifying reference intervals in the clinical laboratory: approved guideline. 3rd ed. CLSI document EP28-A3c. Wayne, PA: Clinical and Laboratory Standards Institute; 2008.
4. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002; 106:3143-421.
5. Stone NJ, Robinson JG, Lichtenstein AH et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. *Circulation.* 2014; 129:S1-45.
6. Hollowell JG, Staehling NW, Flanders WD et al. Serum TSH, T_4, and thyroid antibodies in the United States population (1988 to 1994). *J Clin Endocrinol Metab.* 2002; 87:489-99.
7. Wartofsky L, Dickey RA. The evidence for a narrower thyrotropin reference range is compelling. *J Clin Endocrinol Metab.* 2005; 90:5483-8.
8. Lalkhen AG, McCluskey A. Clinical tests: sensitivity and specificity. *Contin Educ Anaesth Crit Care Pain*. 2008; 8:221-3.
9. Weinstein S, Obuchowski NA, Lieber ML. Clinical evaluation of diagnostic tests. *AJR Am J Roetgenol.* 2005; 184:14-9.
10. Kerruish NJ, Robertson SP. Newborn screening: new developments, new dilemmas. *J Med Ethics.* 2005; 31:393-8.
11. Holmstrom B, Johansson M, Bergh A et al. Prostate specific antigen for early detection of prostate cancer: longitudinal study. *BMJ.* 2009; 339:b3537.
12. Kwon C, Farrell PM. The magnitude and challenge of false-positive newborn screening test results. *Arch Pediatr Adolesc Med*. 2000; 154:714-8.
13. Young DS. Implementation of SI units for clinical laboratory data. *Ann Intern Med.* 1987; 106:114-29.
14. Evans MI, Galen RS, Britt DW. Principles of screening. *Semin Perinatol.* 2005; 29:364-6.
15. Boardman LA, Peipert JF. Screening and diagnostic testing. *Clin Obstet Gynecol.* 1998; 41:267-74.
16. Rembold CM. Number needed to screen: development of a statistic for disease screening. *BMJ.* 1998; 317:307-12.
17. Hendrick RE, Helvie MA. Mammography screening: a new estimate of number needed to screen to prevent one breast cancer death. *AJR Am J Roetgenol.* 2012; 198:723-8.
18. Plebani M. Quality indicators to detect pre-analytical errors in laboratory testing. *Clin Biochem Rev.* 2012; 33:85-8.
19. Rughwani N. Normal anatomic and physiologic changes with aging and related disease outcomes: a refresher. *Mt Sinai J Med.* 2011; 78:509-14.
20. Tietz NW, Shuey DF, Wekstein DR. Laboratory values in fit aging individuals-sexagenarians through centenarians. *Clin Chem*. 1992; 38:1167-85.
21. Favaloro EJ, Franchini M, Lippi G. Aging hemostasis: changes to laboratory markers of hemostasis as we age—a narrative review. *Semin Thromb Hemost.* 2014; 40:621-33.
22. Edwards N, Baird C. Interpreting laboratory values in older adults. *Medsurg Nurs.* 2005; 14:220-9.
23. Fraser CG. Age-related changes in laboratory test results. *Drugs Aging.* 1993; 3:246-57.
24. Duthie EH, Abbasi AA. Laboratory testing: current recommendations for older adults. *Geriatrics.* 1991; 46:41-50.
25. Kelso T. Laboratory values in the elderly. Are they different? *Emerg Med Clin North Am.* 1990; 8:241-54.

26. Tietz NW, Wekstein DR, Shuey DF et al. A two-year longitudinal reference range study for selected serum enzymes in a population more than 60 years of age. *J Am Geriatr Soc.* 1984; 32:563-70.
27. Siest G. Study of reference values and biological variation: a necessity and a model for preventive medicine centers. *Clin Chem Lab Med.* 2004; 42:810-6.
28. Hoppe CC. Prenatal and newborn screening for hemoglobinopathies. *Int J Lab Hematol.* 2013; 35:297-305.
29. Howes RE, Piel FB, Patil AP et al. G6PD deficiency prevalence and estimates of affected populations in malaria endemic countries: a geostatistical model-based map. *PLOS Medicine.* 2012; 9:e1001339.
30. Caraco Y. Genes and the response to drugs. *N Engl J Med.* 2004; 351:2867-9.
31. Nguyen A, Desta Z, Flockhart DA. Enhancing race-based prescribing precision with pharmacogenomics. *Clin Pharmacol Ther.* 2007; 81:323-5.
32. Prandota J. Advances of molecular clinical pharmacology in gastroenterology and hepatology. *Am J Ther.* 2010; 17:e137-62.
33. Smolensky MH, Peppas NA. Chronobiology, drug delivery, and chronotherapeutics. *Adv Drug Deliv Rev.* 2007; 59:828-51.
34. Mendoza J, Challet E. Brain clocks: from the suprachiasmatic nuclei to a cerebral network. *Neuroscientist.* 2009; 15:477-88.
35. Edery I. Circadian rhythms in a nutshell. *Physiol Genomics.* 2000; 3:59-74.
36. Rivkees SA. Mechanisms and clinical significance of circadian rhythms in children. *Curr Opin Pediatr.* 2001; 13:352-7.
37. Rivera-Coll A, Fuentes-Arderiu X, Diez-Noguera A. Circadian rhythms of serum concentrations of 12 enzymes of clinical interest. *Chronobiol Int.* 1993; 10:190-200.
38. Rivera-Coll A, Fuentes-Arderiu X, Diez-Noguera A. Circadian rhythmic variations in serum concentrations of clinically important lipids. *Clin Chem.* 1994; 40:1549-53.
39. Wuerzner G, Firsov D, Bonny O. Circadian glomerular function: from physiology to molecular and therapeutical aspects. *Nephrol Dial Transplant*. 2014; 29:1475-80.
40. Beauchamp D, Labrecque G. Chronobiology and chronotoxicology of antibiotics and aminoglycosides. *Adv Drug Deliv Rev.* 2007; 59:896-903.
41. Otsuka K, Cornelissen G, Halberg F. Circadian rhythms and clinical chronobiology. *Biomed Pharmacother*. 2001; 55:s7-18.
42. Singh R, Sharma PK, Malviya R. Review on chronotherapeutics—a new remedy in the treatment of various diseases. *Eur J Bio Sci.* 2010; 2:67-76.
43. Soldin OP. Thyroid function testing in pregnancy and thyroid disease. *Ther Drug Monit.* 2006; 28:8-11.
44. Costantine MM. Physiologic and pharmacokinetic changes in pregnancy. *Front Pharmacol.* 2014; 5:65.
45. Sullivan KM, Mei Z, Grummer-Strawn L et al. Haemoglobin adjustments to define anemia. *Trop Med Int Health.* 2008; 13:1267-71.
46. Gutierres SL, Welty TE. Point-of-care testing: an introduction. *Ann Pharmacother.* 2004; 3:119-25.
47. Gilbert HC, Szokol JW. Point of care technologies. *Int Anesthesiol Clin.* 2004; 42:73-94.
48. Howick J, Cals JWL, Jones C et al. Current and future use of point-of-care tests in primary care: an international survey in Australia, Belgium, the Netherlands, the UK and the USA. *BMJ Open*. 2014; 4:e005611.
49. Medicare, Medicaid, and CLIA Programs; Extension of Certain Effective Dates for Clinical Laboratory Requirements under CLIA: final rule. *Federal Register.* 1998; 63:55031-4.
50. American Thoracic Society; CDC, and Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR Recomm Rep.* 2003; 52:1-77.
51. Saukkonen JJ, Cohn DL, Jasmer RM et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med.* 2006; 174:935-52.
52. Pene F, Courtine E, Cariou A et al. Toward theragnostics. *Crit Care Med.* 2009; 37:S50-8.
53. Moyer VA. Screening for prostate cancer: US Preventive Services Task Force Recommendation statement. *Ann Intern Med.* 2012; 157:120-34.

BIBLIOGRAPHY

Bakerman S, Bakerman P, Strausbauch P. Bakerman's ABCs of interpretive laboratory data. 5th ed. Scottsdale, AZ: Interpretive Laboratory Data Inc; 2014.

Fischbach FT, Dunning MB. A manual of laboratory and diagnostic tests. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2015.

Jacobs DS, DeMott WR, Oxley DK. Laboratory test handbook with key word index. 5th ed. Hudson, OH: Lexi-Comp Inc; 2001.

Jacobs DS, Oxley DK, DeMott WR. Laboratory test handbook concise with disease index. 3rd ed. Hudson, OH: Lexi-Comp Inc; 2004.

Kraemer HC. Evaluating medical tests. Newbury Park, CA: Sage Publications; 1992.

Laposata M. Laboratory medicine: the diagnosis of disease in the clinical laboratory. 2nd ed. New York: McGraw-Hill Companies Inc; 2014.

Sacher RA, McPherson RA. Widmann's clinical interpretation of laboratory tests. 11th ed. Philadelphia: FA Davis Company; 2000.

Speicher CE. The right test: a physician's guide to laboratory medicine. 3rd ed. Philadelphia: WB Saunders; 1998.

Williamson MA, Snyder LM. Wallach's interpretation of diagnostic tests. 10th ed. Philadelphia: Lippincott Williams & Wilkins; 2015.