Ranbir Chander Sobti ·
Haruhiko Sugimura ·
Aastha Sobti *Editors*

Molecular Biomarkers for Cancer Diagnosis and Therapy

Springer

Molecular Biomarkers for Cancer Diagnosis and Therapy

Ranbir Chander Sobti •
Haruhiko Sugimura • Aastha Sobti
Editors

Molecular Biomarkers for Cancer Diagnosis and Therapy

Springer

Editors
Ranbir Chander Sobti
Department of Biotechnology
Panjab University
Chandigarh, India

Aastha Sobti
Department of Immunotechnology
Lund University
Lund, Sweden

Haruhiko Sugimura
Sasaki Foundation Sasaki Institute
Chiyoda, Tokyo, Japan

ISBN 978-981-99-3745-5 ISBN 978-981-99-3746-2 (eBook)
https://doi.org/10.1007/978-981-99-3746-2

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

Introduction

Cancer has the higher mortality rate in both developed and developing countries and thus poses a serious global health concern (Gopal and Sharpless 2021). Even though there has been a substantial development in the basic understanding of the biology of cancer initiation and progression, identification of cancer risk and successful treatment for various cancers still remain as challenges. The cancer biomarker is a phenotypic attribute that is produced in response to cancer by transformed cells or other cells in the body or under certain benign (noncancerous) conditions (de Martel et al. 2020). Cancer biomarkers typically differentiate cancer-affected patients from the normal populations. Documented alterations in cancer can be due to multiple factors like germline or somatic mutations, transcriptional changes, and post-translational modifications. These alterations are vital targets of biomarkers for the early detection, screening, and identification of cancer (van Gool et al. 2017; Costantini et al. 2020; Chatterjee et al. 2005).

For many decades, the imaging of biopsied samples has been the backbone of cancer diagnostics. Despite numerous advancements in imaging techniques, there remains an intra-observational subjectivity that limits cancer detection in the earlier stages (Flaherty et al. 2012). For early-stage detection, screening tools must have a high level of sensitivity (ability to correct identification of diseased people) and specificity (ability to correct identification of normal people) (Chen et al. 2020). When a test is highly sensitive, it will detect the majority of people who have the disease, resulting in very few false-negative results. When a test is highly specific, only a small percentage of people who do not have the disease will test positive. They should also be widely distributed, acceptable, affordable, and safe (Pepe et al. 2016).

A prognostic biomarker informs about a likely cancer outcome (i.e., disease recurrence, disease progression, death) independent of treatment received. Examples of prognostic biomarkers are prostate-specific antigen (PSA) level at the time of a prostate cancer diagnosis or the PIK3CA mutation status of tumors in women with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer. The majority of tumor diagnostic markers are generated by both normal and cancer cells, but they are formed at much higher levels in cancerous conditions. Some cancer patients' blood, urine, stool, tumor tissue, or other tissues or bodily fluids contain these substances (Wirth et al. 1993; Nagpal et al. 2016).

To date, no tumor marker has been identified that is sensitive or specific enough to be used alone to screen for cancer. For example, men are often screened for prostate cancer using the prostate-specific antigen (PSA) test, which quantifies PSA levels in the blood. The higher PSA level is considered as a tumor marker for prostate cancer (Wirth et al. 1993). CA-125 is a tumor marker that is sometimes elevated in the blood of women with ovarian cancer but can also be elevated in women with benign conditions and thus is not sensitive or specific enough to be used in screening for ovarian cancer in women at average risk (Nagpal et al. 2016).

The advancement of cancer biology has established that oncogenes and tumor-suppressor gene mutations can be identified in body fluids that drain from tumors of affected organs. Measurements of point mutations, loss-of-heterozygosity, and chromosomal aberrations can be obtained from sputum, saliva, and urine with novel assays (Huang et al. 2016). For example, there are molecular assays that have identified p53 and ras mutations from stool and urine samples of cancer patients (von Knebel Doeberitz and Lacroix 1999; Sidransky 1997; Sidransky et al. 1991). Detection of anti-apoptotic proteins (e.g., survivin) in the urine appears to provide a simple, noninvasive diagnostic test to identify patients with new or recurrent bladder cancer (Smith et al. 2001). DNA degradation into 180–200 base pair fragments is a hallmark of apoptosis, and resistance to apoptosis is recognized as a mechanism for the proliferation of cancer cells (Wyllie 1980; Paweletz et al. 2001). Human DNA in normal stools is primarily in fragmented or "short" form. However, stools from patients with colorectal neoplasia have been shown to contain subsets of both non-apoptotic or long DNA arising from dysplastic or anti-apoptotic cells and short DNA from normal mucosa (Ahlquist et al. 2000). The present book covers many of the topics concerning discovery, types, and application of markers in the management of cancers.

RCS is thankful to help rendered by his colleagues and friends in compiling this volume.

He also acknowledges support he received from his wife Dr Vipin Sobti, daughters Er Aditi and Dr Aastha and their spouses Er Vineet and Er Ankit.

Loveable thanks to his granddaughter Irene for her encouragement in the form of a nice smile.

RCS is also thankful to Indian National Science Academy, New Delhi, for providing a platform as Senior Scientist and to Panjab University as an Emeritus Professor to continue academic pursuits.

Chandigarh, India — Ranbir Chander Sobti
Chiyoda, Tokyo, Japan — Haruhiko Sugimura
Lund, Sweden — Aastha Sobti

References

Ahlquist DA, Skoletsky JE, Boynton KA, Harrington JJ, Mahoney DW, Pierceall WE, Thibodeau SN, Shuber AP (2000) Colorectal cancer screening by detection of altered human DNA in stool: feasibility of a multitarget assay panel. Gastroenterology 119(5):1219–1227. https://doi.org/10.1053/gast.2000.19580. PMID: 11054379

Chatterjee SK, Zetter BR (2005) Cancer biomarkers: knowing the present and predicting the future. Future Oncol 1(1):37–50. https://doi.org/10.1517/14796694.1.1.37. PMID: 16555974

Chen X, Gole J, Gore A, He Q, Lu M, Min J, Yuan Z, Yang X, Jiang Y, Zhang T, Suo C, Li X, Cheng L, Zhang Z, Niu H, Li Z, Xie Z, Shi H, Zhang X, Fan M, Wang X, Yang Y, Dang J, McConnell C, Zhang J, Wang J, Yu S, Ye W, Gao Y, Zhang K, Liu R, Jin L (2020) Non-invasive early detection of cancer four years before conventional diagnosis using a blood test. Nat Commun 11(1):3475. https://doi.org/10.1038/s41467-020-17316-z. PMID: 32694610; PMCID: PMC7374162

Costantini S, Budillon A (2020) New prognostic and predictive markers in cancer progression. Int J Mol Sci 21(22):8667. https://doi.org/10.3390/ijms21228667. PMID: 33212936; PMCID: PMC7698401

de Martel C, Georges D, Bray F, Ferlay J, Clifford GM (2020) Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. Lancet Glob Health 8(2):e180–e190. https://doi.org/10.1016/S2214-109X(19)30488-7. Epub 2019 Dec 17. PMID: 31862245

Flaherty KT, Infante JR, Daud A et al (2012) Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med 367(18):1694–1703

Gopal S, Sharpless NE (2021) Cancer as a global health priority. JAMA. https://doi.org/10.1001/jama.2021.12778. PMID: 34357387

Huang CJ, Jiang JK, Chang SC, Lin JK, Yang SH (2016) Serum CA125 concentration as a predictor of peritoneal dissemination of colorectal cancer in men and women. Medicine (Baltimore). 95(47):e5177. https://doi.org/10.1097/MD.0000000000005177. PMID: 27893659; PMCID: PMC5134852

Nagpal M, Singh S, Singh P, Chauhan P, Zaidi MA (2016) Tumor markers: a diagnostic tool. Natl J Maxillofac Surg 7(1):17–20. https://doi.org/10.4103/0975-5950.196135. PMID: 28163473; PMCID: PMC5242068

Paweletz CP, Charboneau L, Bichsel VE, Simone NL, Chen T, Gillespie JW, Emmert-Buck MR, Roth MJ, Petricoin III EF, Liotta LA (2001) Reverse phase protein microarrays which capture disease progression show activation of pro-survival pathways at the cancer invasion front. Oncogene 20(16):1981–1989. https://doi.org/10.1038/sj.onc.1204265. PMID: 11360182

Pepe MS, Janes H, Li CI, Bossuyt PM, Feng Z, Hilden J (2016) Early-phase studies of biomarkers: what target sensitivity and specificity values might confer clinical utility? Clin Chem 62(5):737–742. https://doi.org/10.1373/clinchem.2015.252163. Epub 2016 Mar 21. PMID: 27001493; PMCID: PMC5003106

Sidransky D (1997) Nucleic acid-based methods for the detection of cancer. Science 278(5340):1054–1059. https://doi.org/10.1126/science.278.5340.1054. PMID: 9353179

Sidransky D, Von Eschenbach A, Tsai YC, Jones P, Summerhayes I, Marshall F, Paul M, Green P, Hamilton SR, Frost P et al (1991) Identification of p53 gene mutations in bladder cancers and urine samples. Science 252(5006):706–709. https://doi.org/10.1126/science.2024123. PMID: 2024123

Smith SD, Wheeler MA, Plescia J, Colberg JW, Weiss RM, Altieri DC (2001) Urine detection of survivin and diagnosis of bladder cancer. JAMA 285(3):324–328. https://doi.org/10.1001/jama.285.3.324. PMID: 11176843

van Gool AJ, Bietrix F, Caldenhoven E, Zatloukal K, Scherer A, Litton JE, Meijer G, Blomberg N, Smith A, Mons B, Heringa J, Koot WJ, Smit MJ, Hajduch M, Rijnders T, Ussi A (2017) Bridging the translational innovation gap through good biomarker practice. Nat Rev Drug Discov 16(9):587–588. https://doi.org/10.1038/nrd.2017.72. Epub 2017 Apr 28. PMID: 28450744

von Knebel Doeberitz M, Lacroix J (1999) Nucleic acid based techniques for the detection of rare cancer cells in clinical samples. Cancer Metastasis Rev 18(1): 43–64. https://doi.org/10.1023/a:1006208303075. PMID: 1050554

Wirth M, Manseck A, Heimbach D (1993) Value of prostate-specific antigen as a tumor marker. Eur Urol 24 Suppl 2:6–12. https://doi.org/10.1159/000474380. PMID: 7505232

Wyllie AH (1980) Glucocorticoid-induced thymocyte apoptosis is associated with endogenous endonuclease activation. Nature 284(5756):555–556. https://doi.org/10.1038/284555a0. PMID: 6245367

Contents

Editors and Contributors

About the Editors

Ranbir Chander Sobti is a Senior Scientist, Indian National Science Academy (INSA) and Emeritus Professor at Punjab University. He is a former Vice-Chancellor of Panjab University, Chandigarh & Babasaheb Bhimrao Ambedkar University (Central University), Lucknow. He started his career as a cytogeneticist and then moved on to molecular biology, including genomics, to understand the susceptibility and disease process of cancer, COPD, AIDS, metabolic syndrome, and kidney diseases. He has also used stem cells and nanoparticles to understand the process of tissue organ development through a designed de-cellularization protocol. He has published more than 350 research articles in the journals of international repute and has also published more than 50 books. He is a Fellow of the Third World Academy of Sciences, National Academy of Sciences India, Indian National Science Academy, National Academy of Medical Sciences, National Academy of Agricultural Sciences, Canadian Academy of Cardiovascular Diseases, and few others. He was the General President of the Indian Science Congress Association for the 102nd session held at the University of Jammu in 2013. Dr. Sobti is the recipient of many prestigious awards like the INSA Young Scientist Medal, UGC Career Award, Punjab Rattan Award, JC Bose Oration and Sriram Oration Awards and Life Time Achievement Awards of the Punjab Academy of Sciences, Zoological Society of India, and the Environment Academy of India. He is the recipient of the most prestigious civil award Padmashri of the Government of India.

Haruhiko Sugimura has served as a Chairman and Vice Director, Hammatsu University School of Medicine for 32 years, and now a Professor Emeritus of Hamamatsu University School of Medicine. He had been a President of Japan Cancer Epidemiology and Molecular Epidemiology. He is an internationally recognized cancer biologist, molecular epidemiologist, and molecular pathologist. He had also worked at the University of Tokyo and had been visiting fellow at NCI, NIH Bethesda, from 1988 to 1990. He has published a large number of papers in journals of repute with high impact factor. Currently he serves as a Director of Sasaki Institute, a 140 years old renowned cancer institute in Tokyo.

Aastha Sobti received her BDS from Panjab University, Master's in Clinical Dentistry from the University of London, and Ph.D. from Lund University, Sweden. She carried out her research for Ph.D. at the Department of Immunotechnology, Lund University, Lund, Sweden, under CanFaster, Marie Skłodowska-Curie COFUND program. She has a background in dental sciences and did a specialization in master's in Clinical Dentistry (Oral surgery) from Eastman College, UCL, London. Her core interests are head and neck cancer-based clinical research, in entirety aiding in the field to bring reforms that are required in the present multifarious surgical as well as translational research areas. She has teaching and research experience of about 8 years and published a few papers in international journals of repute. She is a recipient of a large number of prizes and medals for her exceptional work, namely the academic certificate of excellence from BAOS, UK, and IADR Hatton award (India). Additionally, she has attended and presented papers in international conferences in Hong Kong, Croatia, Brazil, Sweden, UK, Japan, and other countries.

Contributors

Anjali Aggarwal Department of Anatomy, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Aitizaz Ul Ahsan Cell and Molecular Biology Lab, Department of Zoology, Panjab University, Chandigarh, India

Vikas Bachhal Department of Orthopedics, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Sukriti Baweja Department of Molecular and Cellular Medicine, Institute of Liver and Biliary Sciences, New Delhi, India

M. L. B. Bhatt Department of Radiation Oncology, King George's Medical University, Lucknow, India

Muskan Budhwar Cell and Molecular Biology Lab, Department of Zoology, Panjab University, Chandigarh, India

Deep Chakrabarti Department of Radiation Oncology, King George's Medical University, Lucknow, India

Sathyapriya Chandramohan Department of Biochemistry and Molecular Biology, Pondicherry University, Kalapet, Puducherry, India

Vinay Chaudhari Shobhaben Pratapbhai Patel School of Pharmacy & Technology Management, SVKM's Narsee Monjee Institute of Management Studies, Juhu, India

Kapil Chaudhary Department of Urology, PGIMER, Chandigarh, India

Monika Chauhan University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, India
School of Health Sciences and Technology, University of Petroleum and Energy Studies, Dehradun, Uttarakhand, India

Mani Chopra Cell and Molecular Biology Lab, Department of Zoology, Panjab University, Chandigarh, India

N. A. Chugh Department of Biophysics, Basic Medical Sciences Block 2, Panjab University, Chandigarh, India

Uzini Devi Daimary Cancer Biology Laboratory and DBT-AIST International Center for Translational and Environmental Research (DAICENTER), Department of Biosciences and Bioengineering, Indian Institute of Technology (IIT) Guwahati, Guwahati, Assam, India

Sudheer K. Devana Department of Urology, PGIMER, Chandigarh, India

Neha Devi Department of Chemistry and Centre for Advanced Studies in Chemistry, Panjab University, Chandigarh, India

Samriti Dhawan Department of Biotechnology, Goswami Ganesh Dutta Sanatan Dharma College, Chandigarh, India

Neelima Dhingra University Institute of Pharmaceutical Sciences, UGC Centre of Advanced Study (UGC-CAS), Panjab University, Chandigarh, India

Kislay Dimri Department of Radiation Oncology, Government Medical College & Hospital, Chandigarh, India

Isra Ahmad Farouk School of Science, Monash University Malaysia, Bandar Sunway, Selangor, Malaysia

Gauri University School of Pharmaceutical Sciences, Rayat-Bhara University, Mohali, Punjab, India

Sosmitha Girisa Cancer Biology Laboratory and DBT-AIST International Center for Translational and Environmental Research (DAICENTER), Department of Biosciences and Bioengineering, Indian Institute of Technology (IIT) Guwahati, Guwahati, Assam, India

Vijay G. Goni Department of Orthopedics, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Shivani Guleria School of Biological and Environmental Sciences, Shoolini University, Solan, Himachal Pradesh, India

Nidhi Gupta Department of Radiation Oncology, Government Medical College & Hospital, Chandigarh, India

Rahul Gupta Department of Gastroenterology and Hepatology, Shalby Multispeciality Hospital, Mohali, India

Ravi Kr. Gupta Department of Environmental Microbiology, Babasaheb Bhimrao Ambedkar University, Lucknow, India

Shubhangi Gupta Shobhaben Pratapbhai Patel School of Pharmacy & Technology Management, SVKM's Narsee Monjee Institute of Management Studies, Juhu, India

Sabia Handa Department of Ophthalmology, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Akinobu Hayashi Pathology Division, Mie University Hospital, Tsu, Japan

Yoshifumi Hirolkawa Department of Oncologic Pathology, Mie University Graduate School of Medicine, Tsu, Japan

Justin Jacob Department of Anatomy, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Divya Jyoti School of Biological and Environmental Sciences, Shoolini University, Solan, Himachal Pradesh, India

Rakesh Kapoor Department of Radiotherapy and Oncology, Postgraduate Institute of Medical Education and Research, Regional Cancer Centre, Chandigarh, India

Vaishali Kapoor Department of Radiation Oncology, School of Medicine, Washington University, St. Louis, MO, USA
Siteman Cancer Center, St. Louis, MO, USA

Mohak Kataria Department of Orthopedics, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Anil Kaul Health Care Administration, Oklahoma State University Center for Health Sciences, Tulsa, OK, USA

Rashmi Kaul Department of Biochemistry and Microbiology, Oklahoma State University-Center for Health Sciences, Tulsa, OK, USA

Ginpreet Kaur Shobhaben Pratapbhai Patel School of Pharmacy & Technology Management, SVKM's Narsee Monjee Institute of Management Studies, Juhu, India

Jagdeep Kaur Department of Biotechnology, Panjab University, Chandigarh, India

Pushpinder Kaur Department of Surgery, Keck School of Medicine, Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA, USA

Tejinder Kaur Department of Zoology, DAV University, Jalandhar, Punjab, India

Divya Khosla Department of Radiotherapy and Oncology, Postgraduate Institute of Medical Education and Research, Regional Cancer Centre, Chandigarh, India

A. Koul Department of Biophysics, Basic Medical Sciences Block 2, Panjab University, Chandigarh, India

Aviral Kumar Cancer Biology Laboratory and DBT-AIST International Center for Translational and Environmental Research (DAICENTER), Department of Biosciences and Bioengineering, Indian Institute of Technology (IIT) Guwahati, Guwahati, Assam, India

Deepak Kumar Department of Orthopedics, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Ravinder Kumar Department of Zoology, Panjab University, Chandigarh, India

Vijay Kumar Department of Zoology, Panjab University, Chandigarh, India

Ajaikumar B. Kunnumakkara Cancer Biology Laboratory and DBT-AIST International Center for Translational and Environmental Research (DAICENTER), Department of Biosciences and Bioengineering, Indian Institute of Technology (IIT) Guwahati, Guwahati, Assam, India

Sunil Kumar Lal School of Science, Monash University Malaysia, Bandar Sunway, Selangor, Malaysia

Rong Liang Department of Medical Oncology, Guangxi Medical University Cancer Hospital, Nanning, Guangxi, People's Republic of China

Zheng Yao Low School of Science, Monash University, Bandar Sunway, Selangor, Malaysia

Premendu P. Mathur Birla Global University, Bhubaneswar, Orissa, India

Sweety Mehra Cell and Molecular Biology Lab, Department of Zoology, Panjab University, Chandigarh, India

Kiyoshi Misawa Department of Otolaryngology, Hamamatsu University School of Medicine, Hamamatsu, Japan

Yuki Misawa Department of Otolaryngology, Hamamatsu University School of Medicine, Hamamatsu, Japan

Nurhamimah Misuan School of Science, Monash University Malaysia, Bandar Sunway, Malaysia

Shoba Narayan Faculty of Allied Health Sciences, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam, Chengalpattu, Tamil Nadu, India

Nihal University School of Pharmaceutical Sciences, Rayat-Bhara University, Mohali, Punjab, India

Awadhesh K. Pandey Department of Radiation Oncology, Government Medical College & Hospital, Chandigarh, India

Dey Parama Cancer Biology Laboratory and DBT-AIST International Center for Translational and Environmental Research (DAICENTER), Department of

Biosciences and Bioengineering, Indian Institute of Technology (IIT) Guwahati, Guwahati, Assam, India

Tarun Pareek Department of Urology, PGIMER, Chandigarh, India

Riley Pritzlaff Department of Biochemistry and Microbiology, Oklahoma State University-Center for Health Sciences, Tulsa, OK, USA

Rukkumani Rajagopalan Department of Biochemistry and Molecular Biology, Pondicherry University, Kalapet, Puducherry, India

Varsha Rana Cancer Biology Laboratory and DBT-AIST International Center for Translational and Environmental Research (DAICENTER), Department of Biosciences and Bioengineering, Indian Institute of Technology (IIT) Guwahati, Guwahati, Assam, India

Seema Rani Department of Zoology, Hindu Girls College, Sonepat, Haryana, India

Daisy Sahni Department of Anatomy, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Ankita Semwal Department of Anatomy, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Aditya P. Sharma Department of Urology, PGIMER, Chandigarh, India
Advance Urology Centre, PGIMER, Chandigarh, India

Madhu Sharma Cell and Molecular Biology Lab, Department of Zoology, Panjab University, Chandigarh, India

Madhulika Sharma Department of Ophthalmology, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Parul Sharma Department of Biotechnology, Thapar Institute of Engineering and Technology, Patiala, Punjab, India

Ramica Sharma University School of Pharmaceutical Sciences, Rayat-Bhara University, Mohali, Punjab, India

Rinu Sharma University School of Biotechnology, Guru Gobind Singh Indraprastha University Dwarka, New Delhi, India

Shtakshi Sharma Department of Zoology, Panjab University, Chandigarh, India

Siddharth Sharma Department of Biotechnology, Panjab University, Chandigarh, India
The Department of Biotechnology, Thapar Institute of Engineering & Technology, Patiala, India

Vinit Sharma Department of Anatomy, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Vishal Sharma Department of Biotechnology, Panjab University, Chandigarh, India

Abhay Kumar Singh Department of Radiation Oncology, School of Medicine, Washington University, St. Louis, MO, USA

Gurfateh Singh Department of Pharmacology, University Institute of Pharmaceutical Sciences, Chandigarh University, Mohali, Punjab, India

Navneet Singh The Department of Pulmonary Medicine, Post Graduate Institute of Medical Education & Research (PGIMER), Chandigarh, India

Prabhjot Singh Centre for Nanoscience and Nanotechnology, Panjab University, Chandigarh, India

Ramandeep Singh Department of Ophthalmology, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Usha Singh Department of Ophthalmology, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Aditya Kumar Singla Department of Radiotherapy and Oncology, Postgraduate Institute of Medical Education and Research, Regional Cancer Centre, Chandigarh, India

Ranbir Chander Sobti Department of Biotechnology, Panjab University, Chandigarh, India

Geetika Suyal University School of Biotechnology, Guru Gobind Singh Indraprastha University Dwarka, New Delhi, India

Hiroyuki Suzuki Hiroyuki Dental Clinic of Oral Surgery, Hamamatsu, Japan
Sasaki Institute, Sasaki Foundation, Tokyo, Japan

Sameeksha Tadepalli Department of Ophthalmology, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Kanika Thakur Department of Zoology, Panjab University, Chandigarh, India

Manish Thakur Department of Microbiology, School of Bio Engineering and Biosciences, Lovely Professional University, Phagwara, Punjab, India

Suheta Tikoo University School of Pharmaceutical Sciences, Rayat-Bhara University, Mohali, Punjab, India

Hardeep S. Tuli Department of Biotechnology, Maharishi Markandeshwar (Deemed to be University), Mullana, India

Jasmeet Singh Tuteja Department of Radiation Oncology, King George's Medical University, Lucknow, India

Eri Usugi Department of Oncologic Pathology, Mie University Graduate School of Medicine, Tsu, Japan

Amisha Vora Shobhaben Pratapbhai Patel School of Pharmacy & Technology Management, SVKM's Narsee Monjee Institute of Management Studies, Juhu, India

Nishima Wangoo Department of Applied Sciences, University Institute of Engineering and Technology (U.I.E.T.), Panjab University, Chandigarh, India

Masatoshi Watanabe Department of Oncologic Pathology, Mie University Graduate School of Medicine, Tsu, Japan

Michelle Khai Khun Yap School of Science, Monash University Malaysia, Bandar Sunway, Malaysia

Ashley Jia Wen Yip School of Science, Monash University, Bandar Sunway, Selangor, Malaysia

Nur Zawanah Zabidi School of Science, Monash University Malaysia, Bandar Sunway, Malaysia

Molecular Biomarkers of Cancer and Their Diagnostic Applications

1

Aitizaz Ul Ahsan, Sweety Mehra, Ranbir Chander Sobti, and Mani Chopra

Abstract

Cancer, characterized by abnormal cell growth, remains a significant global health concern. The intricate interplay of genetic, epigenetic, and proteomic components is intricately linked to cancer progression and persistence. Molecular biology research in the field of cancer is rapidly advancing, leading to fruitful investigations in cancer diagnosis, prognosis, and monitoring. Molecular cancer biomarkers have emerged as crucial elements in cancer biology, with their discovery and implications revolutionizing the field. However, the successful translation of this wealth of information into effective cancer monitoring and treatment poses a major challenge. This chapter provides a comprehensive overview of the diverse types of cancer biomarkers, highlighting recent advancements, addressing associated challenges, and discussing the clinical implications of molecular cancer biomarkers. By delving into these topics, this chapter aims to enhance our understanding of the potential of molecular biomarkers in advancing cancer management strategies.Nowadays, abnormal cell growth also known as cancer is a major global concern. The functional intricacy of genetic, epigenetic, and proteomic components has been associated with the progression and persistence of particular cancer. Molecular biology dealing with cancer is advancing with the progression of cancer, and new investigations are fruitful in the diagnosis, prognosis, and monitoring of cancer. The discovery and implications of molecular cancer biomarkers play a vital role in cancer biology. Over time, novel cancer biomarkers are being developed on the basis of cancer type, but the major challenge is the translation of achieved

A. U. Ahsan · S. Mehra · M. Chopra (✉)
Cell and Molecular Biology Lab, Department of Zoology, Panjab University, Chandigarh, India

R. C. Sobti
Department of Biotechnology, Panjab University, Chandigarh, India

R. C. Sobti et al. (eds.), *Molecular Biomarkers for Cancer Diagnosis and Therapy*,
https://doi.org/10.1007/978-981-99-3746-2_1

information in successful monitoring and curing of cancer. Therefore, this chapter will summarize the various types of cancer biomarkers, advancements, challenges, and clinical implications of molecular cancer biomarkers.

Keywords

Cancer · Biomarkers · Diagnosis of cancer

1.1 Introduction

Cancer has the higher mortality in both developed and developing countries and thus poses a serious global health concern (Gopal and Sharpless 2021). Even though there has been a substantial development in the basic understanding of the biology of cancer initiation and progression, the successful treatment for various cancers and identification of cancer risk remains the challenge. The cancer biomarker is a phenotypic attribute that is produced in response to cancer by cancerous cells or other cells in the body or certain benign (noncancerous) conditions (de Martel et al. 2020). Cancer biomarkers typically differentiate cancer-affected patients from the normal population. Documented alterations in cancer can be due to multiple factors like germline or somatic mutations, transcriptional changes, and posttranslational modifications. These alterations are vital targets of biomarkers for the early detection, screening, and identification of cancer (van Gool et al. 2017; Costantini and Budillon 2020; Chatterjee and Zetter 2005).

For many decades, the imaging of biopsied samples has been the backbone of cancer diagnostics. Despite numerous advancements in imaging techniques, there remains an intraobservational subjectivity that limits cancer detection in the earlier stages (Flaherty et al. 2012). For early-stage detection, screening tools must have a high level of sensitivity (ability to correct identification of diseased people) and specificity (ability to correct identification of normal people) (Chen et al. 2020). When a test is highly sensitive, it will detect the majority of people who have the disease, resulting in very few false-negative results. When a test is highly specific, only a small percentage of people who do not have the disease will test positive. They should also be widely distributed, acceptable, affordable, and safe (Pepe et al. 2016).

A prognostic biomarker informs about a likely cancer outcome (i.e., disease recurrence, disease progression, death) independent of treatment received. Examples of prognostic biomarkers are prostate-specific antigen (PSA) level at the time of a prostate cancer diagnosis or the PIK3CA mutation status of tumors in women with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer. The majority of tumor diagnostic markers are generated by both normal and cancer cells, but they are formed at much higher levels in cancerous conditions. Some cancer patients' blood, urine, stool, tumor tissue, or other tissues or bodily fluids contain these substances (Wirth et al. 1993; Nagpal et al. 2016).

To date, no tumor marker has been identified that is sensitive or specific enough to be used alone to screen for cancer. For example, men are often screened for prostate cancer using the prostate-specific antigen (PSA) test, which quantifies PSA levels in the blood. The higher PSA levels (Wirth et al. 1993). CA-125, a tumor marker that is sometimes elevated in the blood of women with ovarian cancer but can also be elevated in women with benign conditions and thus is not sensitive or specific enough to be used in screening for ovarian cancer in women at average risk (Nagpal et al. 2016).

The advancement of cancer biology has established that oncogenes and tumor-suppressor gene mutations can be identified in body fluids that drain from affected organ by the tumor. Measurements of point mutations, loss-of-heterozygosity and chromosomal aberrations can be obtained from sputum, saliva, and urine with novel assays (Huang et al. 2016). For example, there are molecular assays that have identified p53 and ras mutations in stool and urine of cancer patients (von Knebel Doeberitz and Lacroix 1999; Sidransky 1997; Sidransky et al. 1991). Detection of antiapoptotic proteins (e.g., survivin) in the urine appears to provide a simple, noninvasive diagnostic test to identify patients with new or recurrent bladder cancer (Smith et al. 2001). DNA degradation into 180–200 base pair fragments is a hallmark of apoptosis, and resistance to apoptosis is recognized as a mechanism for the proliferation of cancer cells (Wyllie 1980; Paweletz et al. 2001). Human DNA in normal stools is primarily in fragmented or "short" form. However, stools from patients with colorectal neoplasia have been shown to contain subsets of both nonapoptotic or long-DNA arising from dysplastic or antiapoptotic cells and short-DNA from normal mucosa (Ahlquist et al. 2000).

1.2 Advancement and Challenges in Cancer Biomarker Science

1.2.1 Specificity of the Biomarkers

Various tumor markers have been recognized and are nowadays being used in clinical set ups. Some are associated with only one type of cancer, while others are associated with two or more types of cancer. This presents a major challenge to the success of the biomarker. The use of cancer diagnostic markers is not without its drawbacks. Noncancerous conditions sometimes can cause altered levels of tumor markers. Moreover, not everyone with a particular type of cancer has a higher level of a tumor marker associated with that cancer (Mayeux 2004; Sauter 2017). Furthermore, tumor markers have not yet been discovered for all types of cancer. Moreover, cancer biomarkers have not yet been discovered for all forms of tumors. Even if an elevated level of a tumor marker may indicate the presence of cancer, it is not perfectly adequate for cancer diagnosis (Henry and Hayes 2012). As a result, tumor marker assessments are commonly used in accordance with other tests, such as biopsies, to diagnose cancer. Before treatment, tumor marker levels can be measured to help doctors plan the best course of action. The level of a diagnostic biomarker can

indicate the stage (amount) of the disease and/or the patient's prognosis in some cancers (likely outcome or course of disease) (Mayeux 2004).

1.2.2 Screening Strategies

A screening strategy must be effective enough in diagnosing malignant cells that are going to grow, differentiate, and ultimately cause death. Unfortunately, little information is available regarding the underlying mechanism which instigates cancerous cells to become malignant and ultimately lethal transformed cells. On the other hand, complexity of the tissue leads to the development of various types of cancers within same tissue. These factors have significant effects on the effectiveness of biomarkers (Bast Jr et al. 2020; Baron 2012).

1.2.3 Inheritance of Particular Cancer

Various researches over time have revealed that inheritance of cancer is not instant and particular mutation causing may take decades to be lethal. Most cancers exhibit genomic instability and need multiple environmental and genetic hits to spread to other parts of the body (Urbach et al. 2012). For example, in the case of pancreatic cancer, the cells take at least a decade in transforming into metastatic cells. This usually affects the performance of the cancer biomarkers and still needs to be investigated properly to overcome the hurdles in designing the appropriate biomarker (Yachida et al. 2010).

1.2.4 Identification and Monitoring of Biomarkers

Most tumor markers are proteins. However, more recently, alterations to DNA have also begun to be used as tumor markers. As we know, cancers are induced by a cascade of genetic and/or epigenetic changes that lead to changes in the expression levels of proteins in the affected cells (Takeshima and Ushijima 2019). Protein alterations can have an impact on cell metabolism and physiology, cell growth and death, and the secretion of molecules that communicate with other cells and tissues. The biomarkers include genes and genetic variations, differences in messenger RNA (mRNA) and/or protein expression, and posttranslational modifications of proteins and metabolite levels. Thus, the genomic, proteomic, and metabolomic biomarkers may be used to diagnose cancer, and track the disease progression and therapeutic response (Tainsky 2009). Biomarker discovery can be done using both hypothesis-driven and technology-driven approaches. The commonly used genomic technologies include DNA microarrays, PCR-based assays, and fluorescence *in situ* hybridization (FISH). The molecular markers and diagnostic imaging are complementing each other for biomarker research and now the tumor markers may be measured periodically during cancer therapy via many technologies. A decline in

Table 1.1 Different cancer biomarkers and their diagnostic use (Adapted from, Vaidyanathan and Vasudevan 2012)

Sr. no.	Marker	Cancer type	Tissue analyzed	Diagnostic role
1.	*ALK gene rearrangements and over-expression*	Nonsmall cell lung cancer and anaplastic large cell lymphoma	Tumor	Treatment and prognosis
2.	*Alpha-fetoprotein (AFP)*	Liver cancer and germ cell tumors	Blood	Diagnosis, To check the efficacy of treatment against cancer and assessment of recurrence
3.	*Beta 2-microglobulin (B2M)*	Multiple myeloma, chronic lymphocytic leukemia, and some lymphomas	Blood, urine, or cerebrospinal fluid	Prognosis and follow response to treatment
4.	*Beta-human chorionic gonadotropin (Beta-hCG)*	Choriocarcinoma and germ cell tumors	Urine or blood	Assessment of stage, prognosis, and response to treatment
5.	*BRCA1 and BRCA2 gene mutations*	Ovarian cancer	Blood	To check the efficacy of treatment against cancer and assessment of recurrence
6.	*BCR–ABL fusion gene (Philadelphia chromosome)*	Chronic myeloid leukemia, Acute lymphoblastic leukemia, Acute myelogenous leukemia	Blood and/or bone marrow	Confirmation of diagnosis, predict response to targeted therapy, monitor disease status
7.	*BRAF V600 mutations*	Cutaneous melanoma and colorectal cancer	Tumor	To select the patients who are most likely to benefit from treatment with certain targeted therapies
8.	*C-kit/CD117*	Gastrointestinal stromal tumor and mucosal melanoma	Tumor	Diagnosis and treatment
9.	*CA15-3/CA27.29*	Breast cancer	Blood	To check the efficacy of treatment against cancer
10.	*CA19-9*	Pancreatic, gall bladder, bile duct, and gastric cancer	Blood	To check the efficacy of treatment against cancer
11.	*CA-125*	Ovarian cancer	Blood	Diagnosis, assessment of response to treatment, and evaluation of recurrence

(continued)

Table 1.1 (continued)

Sr. no.	Marker	Cancer type	Tissue analyzed	Diagnostic role
12.	*Calcitonin*	Medullary thyroid cancer	Blood	Diagnosis, To check the efficacy of treatment against cancer and assessment of recurrence
13.	*Carcinoembryonic antigen (CEA)*	Colorectal cancer and some other cancers	Blood	Diagnosis, To check the efficacy of treatment against cancer and assessment of recurrence
14.	*CD20*	Non-Hodgkin lymphoma	Blood	To check the efficacy of treatment against cancer and assessment of recurrence
15.	*Chromogranin A (CgA)*	Neuroendocrine tumors	Blood	Diagnosis, To check the efficacy of treatment against cancer and assessment of recurrence
16.	*Chromosome 3, 7, 17, and p21*	Bladder cancer	Urine	Monitoring for tumor recurrence
17.	*Circulating tumor cells of epithelial origin (CELLSEARCH®)*	Metastatic breast, prostate, and colorectal cancers	Blood	To inform clinical decision making and prognosis of cancer
18.	*Cytokeratin fragment 21-1*	Lung cancer	Blood	Monitoring for recurrence
19.	*EGFR gene mutation analysis*	Nonsmall cell lung cancer	Tumor	Treatment and prognosis
20.	*Estrogen receptor (ER)/progesterone receptor (PR)*	Breast cancer	Tumor	To check the efficacy of treatment with hormone therapy against cancer and assessment of cancer recurrence
21.	*Fibrin and fibrinogen*	Bladder cancer	Urine	Monitoring of progression and response to treatment
22.	*HE4*	Ovarian cancer	Blood	Cancer treatment planning, assessment of disease progression and monitoring for recurrence
23.	*HER/neu gene amplification or protein overexpression*	Breast cancer, gastric cancer, and gastroesophageal	Tumor	To check the efficacy of treatment with certain targeted therapies

(continued)

Table 1.1 (continued)

Sr. no.	Marker	Cancer type	Tissue analyzed	Diagnostic role
		junction adenocarcinoma		
24.	*Immunoglobulins*	Multiple myeloma and Waldenstrom macroglobulinemia	Blood and urine	Diagnosis, Assessment of response to treatment, and look for recurrence
25.	*KRAS gene mutation analysis*	Colorectal cancer and nonsmall cell lung cancer	Tumor	To check the efficacy of treatment with certain targeted therapies
26.	*Neuron-specific enolase (NSE)*	Small cell lung cancer and neuroblastoma	Blood	Diagnosis and to assess response to treatment
27.	*Nuclear matrix protein 22*	Bladder cancer	Urine	To monitor response to treatment
28.	*Programmed death ligand 1 (PD-L1)*	Nonsmall cell lung cancer	Tumor	To check the efficacy of treatment with certain targeted therapies
29.	*Prostate-specific antigen (PSA)*	Prostate cancer	Blood	Diagnosis, Assessment of response to treatment, and look for recurrence
30.	*Thyroglobulin*	Thyroid cancer	Blood	To check the efficacy of treatment with hormone therapy against cancer and assessment of cancer recurrence
31.	*Urokinase plasminogen activator Upa and plasminogen activator inhibitor (PAI-1)*	Breast cancer	Tumor	Cancer progression and look for recurrence

the level of a diagnostic biomarker or a return to the normal level of the marker may indicate that the carcinoma is responding to treatment, whereas no transformation may reflect that the cancer is not responding to the treatment. After treatment has finished, biomarkers can be measured to check for cancer recurrence (Maruvada et al. 2005; Jain 2013). For a wide range of cancer types, a number of diagnostic markers currently being used are listed below (Table 1.1).

1.3 Clinical Implications of Various Cancer Biomarkers

1.3.1 DNA Methylation as an Epigenetic Cancer Biomarker

DNA methylation and histone modifications confer the heritable changes in cellular phenotype. These epigenetic phenomena play a vital role in DNA-based processes like replication, transcription, and DNA repair and can thus influence tumorigenesis stages, eventually promoting pathogenic neoplastic cells. These changes could be used as prognostic biomarkers in the early stages of cancer diagnosis. Patients with specific cancers that respond to specific cytotoxic chemotherapies will benefit from these biomarkers. These epigenetic modifications are reversible and potentially useful as therapeutic targets (Han et al. 2017). If the genetics or the mutations can provide us the predisposition of a disease, the epigenetics provide us with the current status or activity of disease. The epigenetic alterations are innovative biomarkers for cancer due to their stability, frequency and noninvasive accessibility in bodily fluids such as blood, sweat, urine, saliva, etc. Recently, there has been great attention for aberrant methylated DNA being explored for the possible epigenetic biomarkers to be translated into the clinical application. Multiple studies have investigated global DNA methylation profiles and gene-specific DNA methylation in blood-based DNA to develop powerful screening markers for cancer (Wei et al. 2021).

There is currently a scarcity of noninvasive biomarkers with adequate precision for identifying patients in need of treatment, particularly in the early stages of cancer. The Food and Drug Administration (FDA) has so far approved only SEPT9 for use as a blood-based methylated biomarker for the diagnosis of colon cancer (Leygo et al. 2017). Although, advancements in epigenetics research has led to the improved disease outcome of patients with certain forms of lymphoma and leukemia's by using the drugs that alter DNA methylation and histone acetylation/methylations, more research for optimizing and validating the methylation markers is needed. Among its various challenges, the timing and heterogeneity of methylation as well as the difference in methylation levels between epithelial and stromal tissues in various cancers is a cutting edge window in epigenetic of cancers (Mikeska et al. 2012). Unlike mutation screening, in the pathological aberrations for DNA methylation analysis, a baseline needs to be defined for every region in the appropriate normal control tissues. Furthermore, many gene loci also show an age-dependent increase in DNA methylation. Overall, the choice of region to be studied is one of the critical challenges in establishing a specific DNA methylation biomarker for the clinical use.

1.3.2 Noncoding RNAs (MicroRNAs) as Cancer Biomarkers

The molecular mechanism of long noncoding RNA is strictly based upon controlling the gene expression by direct recruitment of histone modification enzymes to cell chromatin. DNA methylation and the resulting chromatin modifications render the protein product to be functional. The functional abnormality of these epigenetic changes is the key to the development of carcinogenesis. The long noncoding RNA

Table 1.2 miRNAs (miR) with a possible diagnostic use in various cancers

Tumor	Prognostic miRNAs	Diagnostic miRNAs
Breast cancer	miR-335, miR-126	miR-145, miR-195, miR let 7a
Nonsmall cell lung cancer	miR-34a, miR-21, miR let-7a, miR-155	miR-25 miR-223
Colorectal cancer	MiR 34b/c, miR-148a	miR-29a, miR-92a, miR-17, miR-221

(lncRNAs) reveal diverse gene expression profiles in benign and metastatic tumors. Small noncoding RNAs, also known as microRNAs, are capable of reprogramming multiple oncogenic pathways and can thus be used as target agents. MicroRNAs (miRNAs) are small, endogenous noncoding RNAs, 21–24 nucleotides (nt) long, which induce posttranscriptional gene silencing, recognizing their target mRNAs by base complementarity (Hao et al. 2017). They regulate particular target genes and are thus implicated in various biological processes such as proliferation, death, differentiation, motility and invasiveness. The deregulation or genetic changes of miRNAs have been critically implicated in the initiation and progression of most cancers.

By using high-resolution array-based genomic hybridization, the spectrums of cancer-associated miRNAs have been found in various types of cancer cell lines and clinical tumor specimens. The abnormal expression of miRNAs in cancer is correlated to different mechanisms which include chromosomal abnormalities, genomic mutations, polymorphism, epigenetic changes, and alteration in miRNA biogenesis. All these processes have important roles in cancers. The cells are able to actively secrete endogenous miRNAs in serum and other body fluids. Besides finding their roles as oncogenes and tumor suppressors, the various studies suggest that miRNA expression signatures across solid cancers could represent biomarkers in cancer diagnosis. For example, miR-145 has been considered to have potential clinical applications as a novel biomarker for breast cancer diagnosis. Similarly, the miR-25 and miR-223 are more expressed in lung cancer patients. The increasing evidence supports a role for miRNAs as prognostic biomarkers of human cancers and in relation to different types of cancers, the same miRNAs may not have the same role in prognosis (Corsini et al. 2012) (Table 1.2).

However, the miRNA targeting is known to be sequence specific instead of gene specific and gene silencing, and the miRNA requires only a partial complementary between miRNA and protein-coding transcripts (Sohel 2020). Further investigations are needed to specifically evaluate these approaches in various human tumors for the successful clinical use.

1.3.3 Protein Biomarkers in various cancers

Cancer is a genetic disease that develops through the progressive accumulation of activating alterations to growth promoting oncogenes and inactivating alterations to tumor-suppressor genes. These changes result in a marked difference in protein

Table 1.3 Important FDA-approved cancer biomarkers

Sr. No.	Cancer biomarkers	Type of cancer
1.	*CEA*	Malignant pleural effusion
2.	*CEA*	Peritoneal cancer
3.	*Her-2/neu*	Stage IV breast cancer
4.	*Bladder tumor antigen*	Urothelial cell carcinoma
5.	*Thyro-globulin*	Thyroid cancer metastasis
6.	*Alpha-fetoprotein*	Hepatocellular carcinoma
7.	*PSA*	Prostate cancer
8.	*CA 125*	Nonsmall cell lung cancer
9.	*CA19.9*	Pancreatic cancer
10.	*CA 15.3*	Breast cancer
11.	*Leptin, prolactin, osteopontin, and IGF-II*	Ovarian cancer
12.	*CD98, fascin*	Lung cancer

expression between normal and cancerous cells, some of which can be collected from peripheral body fluids and analyzed to determine the status of a tumor *in vivo*. In 1847, Bence-Jones discovered the cancer biomarker proteins and since this discovery, only about ten proteins have progressed to the level of FDA-approved cancer diagnostic markers tests, and the majority of these lack ideal cancer specificity and sensitivity (Anderson et al. 2004). Also the current proteomics technology is limited in its ability to detect low-abundance potential cancer biomarkers against a background of high-abundance plasma proteins, which means that many of the best markers may be missed until discovery technology improves. The intensive research is being conducted to identify biomarkers capable of identifying the populations most at risk for a disease and of detecting the disease before it becomes clinically apparent. Unfortunately, not all the cancers have biomarkers available for clinical or for efficiently screening patients at a high risk (Table 1.3).

Recently, the exosomes which are endosome derived nanometer-sized (30–150 nm) vesicles that are secreted from various types of cells are being studied extensively. As exosomes are stable in peripheral blood, they are a promising tumor-derived material for the characterization of tumor behavior, so exosomes can be monitored and exosome-derived proteins can be used for early diagnosis of various cancers. Since the sensitivity and specificity are the two major standards to be evaluated for the diagnostic marker; however, no study has yet indicated sensitivity and specificity of an exosomal biomarker, so further evaluation needs to be conducted with regard to these (Li et al. 2017). In recent years, other peripheral blood tests such as circulating tumor cells and circulating tumor DNA are also used to make early diagnosis in clinical studies, so the advantage and disadvantage can be compared between circulating tumor cells or DNA and exosome biomarkers in future. Also, more clinical studies are needed to establish a strong correlation between exosome biomarkers, diagnosis and prognosis with their sensitivity as well as specificity.

Table 1.4 FDA-approved drugs targeting gene fusions in malignant disorder

Gene fusion	Drug	Disease
ALK fusions	Crizotinib	Nonsmall cell lung cancer (NSCLC)
BCR–ABL1	Imatinib	Chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL)
COL1A1–PDGFRB	Imatinib	Dermatofibrosarcoma protuberans (DFSP)
FIP1L1–PDGFRA	Imatinib	Hypereosinophilic syndrome/chronic eosinophilic leukemia (HES/CEL)
PDGFR fusions	Imatinib	Myelodysplastic syndrome/myeloproliferative neoplasm (MDS/MPN)

1.3.4 Fusion Genes in Cancer Diagnostics

These are neoplasia-related mutations that play a key role in tumorigenesis and thus are implicated in malignant hematological diseases and solid tumors. They arise by structural chromosome rearrangements such as chromosomal insertion, deletion translocation, or inversion, which bring together two genes that were previously separated. The integrated gene products from such processes have the potential for cancer development, therefore making them potential prognostic markers in cancer. The prototypic fusion oncogene associated with prolonged myeloid leukemia is the BCR–ABL1 fusion gene found on the well-known Philadelphia (Ph) chromosome (CML). It is now used as a biomarker in the diagnosis and treatment monitoring of patients. It is well established that the oncogenic potential of ETS-related gene (ERG) is involved in Ewing's sarcoma and leukemia. It is also observed that 40–70% of men with castration-resistant prostate cancers have ETS-related gene (ERG) rearrangements, which may respond better to antihormonal therapy than ERG-negative ones. Imatinib is a tyrosine kinase inhibitor and was the first drug that was specifically designed to target a fusion gene, i.e., BCR–ABL1 in CML (Mertens et al. 2015). BRAF, FGFR3, NTRK1, RET, and ROS1 are some kinase encoding regions which show fusions in various cancers. Because more novel drugs involving gene fusions are awaiting FDA approval, stratification of diagnosis and treatment may become increasingly important in clinical practice (Table 1.4). Many technologies such as cytogenetics, fluorescence *in situ* hybridization (FISH), chromosome banding analysis, reverse transcriptase-polymerase chain reaction, and Sanger sequencing are being used in detecting gene fusions and other genetic aberrations. It is better to combine the next-generation sequencing (NGS) result with high-throughput functional cellular assays and more functional data in cancer genomics (Kuchenbauer et al. 2008).