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Cancer Diagnosis and Treatment: An Overview for the General Practitioner

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1. Introduction

Many cancer patients will first present to a primary care provider either in the clinic or acutely in the inpatient setting before a definite diagnosis of cancer is made. Thus, an accurate clinical evaluation - through history taking and physical examination - by a general practitioner could reveal malignant diseases at their early stages. In some instances, cancer is incidentally detected while a patient is being treated for other unrelated diseases. Plain radiographs ordered by the primary care physician for pneumonias or back pains, for instance, have been known to reveal occult lung tumors or bone metastasis.

With advances in cancer treatment, many cancer patients are living into the survivorship period and are increasingly being seen by primary care providers following active treatment. At such times, the primary care provider plays a major role in surveillance, management of cancer treatment complications and treatment of comorbid conditions. A 40 year old woman who has been treated for breast cancer, for example, will still need colorectal cancer screening as well as yearly pap smears from her primary care physician in addition to her required follow up with Breast Oncology.

Since the primary care provider plays such an invaluable role in cancer prevention, detection and control, it is imperative that the primary care provider is kept abreast of the latest advances in the ever evolving field of cancer diagnosis and therapy. While the general practitioner will likely not be responsible for cancer staging and treatment, there might be need for him or her to select the initial screening or diagnostic tests for malignant diseases prior to referral to the cancer specialist. There is therefore need for a concise literature for the generalist on the current and up-to-date approach to the diagnosis and treatment of cancers and hematological diseases.

Current classifications in surgical pathology for staging malignancies are based on anatomic features (tumor-node-metastasis) and histopathology (grade)[1]. Different modalities currently exist for the diagnosis and treatment of cancer. Most have been in use for many years whereas others have evolved as our understanding of the molecular processes that lead to carcinogenesis has increased.

2. Laboratory diagnosis of hematological and oncological diseases

2.1 Morphological methods

Morphological examinations are the easiest methods of cancer diagnosis.[2] Many sophisticated laboratory and imaging techniques have evolved in Oncology over the years but clinician still have to depend on histopathology for the definite diagnosis of many solid tumors. Only in rare occasions have imaging and appropriate biochemical assays substituted microscopic examination of a tissue sample for cancer diagnosis.

Proper pathological diagnosis begins with the referring clinician. Since certain disease processes share similar morphological and microscopic appearances, the clinical information supplied by the requesting medical provider goes a long way in helping the histopathologist to make definitive diagnoses. Proper and complete history must precede all requests for pathological evaluation.

Pertinent patient data that must accompany any tissue sample to the laboratory include the patient identity, age, gender, duration of the disease and exact location of the lesion, size and any previous treatment. With the advent of electronic medical records, the clinician should ensure that these data are in the patient's electronic records from where the pathologist can retrieve them easily as needed.

In addition to appropriate collection and reporting of clinical data to the pathologist, the referring physician must ensure that the pathological specimen is properly obtained from a well selected biopsy site and must be properly handled and transported to the laboratory.

2.2 Sampling methods for pathological exam

Incisional biopsy is easy to perform. It involves the removal of a small part of a large tumor for the purpose of laboratory diagnosis. This method is usually chosen for lesions that are easy to access. Following diagnosis, the tumor is usually completely removed surgically or treated by other modalities.

Excisional biopsy is an alternative to incisional biopsy. It enables a more complete pathological exam of the lesion and thus it is the most appropriate collection method for small tumors. It is also the best method for evaluation of lymph nodes; since pathological changes in lymph nodes may be focal and might be missed when sampled by incisional biopsy[3] . As expected, excisional biopsy might cause more local trauma than incision biopsy.

Needle aspiration allows the clinician to obtain a core of tissue from a mass for cytological examination. It is increasingly being employed for tumors in which there is a visible or readily palpable mass such as lymph nodes, breast or thyroid. Using ultrasound, computed tomography or fluoroscopy guidance, needle aspiration can also be used for deeper organs such as the liver. There is a possible complication of tumor implantation along the tract of the needle.

Cytology is a method that has been used widely in cervical cancer screening and could be employed for other suspected cancers like bladder, gastric and lung cancers. It is based on the premise that neoplastic cells are less cohesive than normal cells and are easily shed into

body fluids such as urine, gastric fluid, pleural, peritoneal and bronchial fluids.[2] With improvement in accessibility of organs by endoscopy, cytological examinations are being largely replaced by direct endoscopy and biopsy of the stomach, bladder, and bronchi.[3] Cytology may still be used in follow up of patients that have been treated for cancers of the bladder or urinary tract. Routine Papanicolaou smears are still the mainstay of cervical cancer screening.

Endoscopic procedures grant access to internal organs thereby enabling biopsy of the internal organs

2.3 Specimen preparation

Following collection of tissue specimen, it undergoes preparation prior to histological exam. Specimen preparation can be permanent or frozen sections.

Permanent method involves the processes of fixation, embedding, sectioning and staining. The tissue specimen is initially fixed in formalin, and then embedded in paraffin wax to preserve its architecture and facilitate sectioning. Sectioning involves cutting the specimen into thin slices that can be examined with the microscope. The micro-sections are then finally stained prior to microscopic examination.

When the pathologist anticipates a different examination modality than histopathology, the choice of fixing and staining agents might be modified as appropriate.

Frozen section is a rapid method that quickly prepares fresh tissue for microscopic examination. It is easily used by surgeon within the operating suite to obtain an immediate pathological interpretation of the specimen and thus decide on the next therapeutic approach to pursue during surgery. It has also enabled surgeons to establish adequacy of excision margins.[3]

2.4 Molecular techniques

The diversity of genomic alterations involved in malignancy had led to the development of a variety of assays for complete tumor profiling. Thus, it is no longer adequate to know the histopathology of a cancer. The new molecular diagnostics when integrated into existing histomorphological classifications in surgical pathology provides additional stratification for a more accurate cancer prognosis.[1]

Detection of molecular markers in neoplastic tissue samples can be used to provide accurate diagnosis, prognosis and prediction of response, resistance, or toxicity to therapy. These molecular markers can be products of altered genes/DNA or abnormal pathways. Mutations in DNA can include rearrangements such as translocations, inversions, gene amplifications/deletions, point mutations and base insertions/deletions.

Cytogenetic procedures study the chromosomes in the tissue sample with the aim to identify any chromosomal changes that are peculiar to known cancer types.

FISH technique is a molecular cytogenetic technique in which probes are used to confirm presence or absence of specific DNA sequences on chromosomes. It is used in diagnosis of blood disorders or cancer which are due to specific genetic alterations on the chromosomes.

PCR is a quantitative technique that permits amplification and analysis of target DNA regions in tumor samples.

DNA microarray analysis is equipped to measure the expression levels of large number of genes concurrently.

Immunocytochemistry (IHC)is used to detect antigens or protein expression on a fixed tissue section by means of an antibody that is specific for the antigen/protein. The antibody-antigen reaction is visualized by linking the antibody to an enzyme that catalyzes a color producing reaction or to a substance that fluoresces. IHC serves as an adjunct to regular histological exam of a tissue sample and is being routinely used to detect the presence of antigens, proteins, and biomarkers in neoplastic tissue samples. It has been employed largely for the detection of estrogen and progesterone receptors on breast tissues, to detect oncogenes and tumor suppressor gene products on tumor samples as well as to characterize leukemias and lymphomas.

Flow cytometry is a technique that is used to examine and differentiate cells based on certain physical and chemical properties. A sample of blood or tissue cells in suspension is passed through the flow cytometer and the scatter emitted by the cell where it meets the light is analyzed to better characterize the cell.

Electron microscopy is used when specific cellular or intracellular structures need to be examined. Like IHC, it aids in a more accurate tumor classification.

Molecular cancer diagnostic techniques have been instrumental to identifying the brc-abl in CML, HER-2/NEU expression in breast cancer.

2.5 Biomarkers

Biomarkers are proteins which are released from cancers and whose detection or increase in the serum may screen or confirm the presence of certain cancers. Biochemical assays for tumor-associated enzymes, hormones and other markers are not being used for the definitive diagnosis of cancer[2]. Instead, cancer biomarkers complement pathological examination and thus play a role in the early detection, outcome prediction and detection of disease recurrence. In addition, in the present era of new therapeutic agents, biomarkers can help to determine which tumors will respond to which treatments.[4] Some biomarkers that are currently in clinical use are shown in **Table 1.**

The ideal biomarker should have a high specificity and sensitivity, especially if it is to be useful for staging [5]. In addition, it should be easily detected in the patient's blood or urine but not in a healthy person. Many of the current biomarkers in clinical practice lack enough sensitivity or specificity to accurately serve as the sole diagnostic tool for the diagnosis of any cancer.

It must be pointed out that despite the detection of biomarkers in a patient, a histological exam is often necessary to confirm cancer.

3. Imaging diagnosis

Histological diagnosis is still essential to establish the diagnosis of cancer. But a well-designed imaging strategy is important in the management of a patient with cancer.

Depending on circumstances, imaging can precede or follow histopathology.[6] The choice of imaging techniques are many and still evolving, and the physician must carefully select the modalities based on a good understanding of the specific neoplasm, its biological characteristics and its response to treatment.[7]

Biomarker	Type	Source	Cancer type	Clinical use
α-FP	glycoprotein	serum	nonseminomatous testicular	staging
HCG-β	glycoprotein	serum	testicular	staging
CA19-9	carbohydrate	serum	pancreatic	monitoring
CA125	glycoprotein	serum	ovarian	monitoring
CEA	protein	serum	colon	monitoring
Thyroglobulin	protein	serum	thyroid	monitoring
PSA	protein	serum	prostate	screening and monitoring
Estrogen receptor	protein	breast tumor	breast	selection for hormonal therapy
Progesterone receptor	protein	breast tumor	breast	selection for hormonal therapy
HER2/NEU	protein	breast tumor	breast	prognosis and selection of therapy
BTA	protein	urine	bladder	monitoring

Adapted from Ludwig JA, Weinstein JN. 2005. Biomarkers in cancer staging, prognosis and selection. *Nature Reviews Cancer* 5 : 845-857.

Table 1. Examples of common biomarkers in clinical use

Imaging in Oncology is used for screening, detection, diagnosis, treatment and to follow response to treatment. The choice of imaging for every type of cancer is beyond the scope of this text. Brief highlights of each of the commonly available imaging modalities will be enumerated.

Conventional radiology is widely available, and cheap. It is however largely being replaced by other techniques like CT and MRI for definition of tumor anatomy. Plain and Contrast radiography (barium or iodine) is still part of initial evaluation of GI pathology.[7] Many cancers have been discovered following radiological tests done for unrelated diseases.

Ultrasound US is relatively cheap and safe. It has become instrumental in guiding procedures such as biopsies and for assessment of fluid collections.

Mammography has become routine for breast cancer screening. This is the commonest imaging technique that is being used for mass screening for cancer.

CT plays a critical role in cancer diagnosis, staging, follow up as well as in relapse of neoplastic disease. It is increasingly being used to guide diagnostic biopsies, as part of radiotherapy simulations.

MRI is a costly imaging method. Like CT, it is useful in diagnosis, staging, therapy and follow up. It is also increasingly being used in minimally invasive procedures. CT is however more widely available.

PET makes use of labeled isotopes active which are tagged to metabolically active substances. When such substances are administered, they concentrate on certain areas of the body and yield imaging studies of metabolism. PET is useful in staging, detecting recurrences and evaluation of several cancers such as head and neck tumors, brain tumors, lymphomas, and colorectal cancers.

The last decade has seen the gradual shift to PET/CT which is an imaging modality that combines anatomy and function. It has become a powerful tool for diagnosis and staging in Oncology. PET-CT combines the functional imaging obtained by PET to the anatomical imaging of CT to a single superimposed image. The patient is therefore saved the time and costs of two separate imaging sessions. Even though this imaging technique was initially used for lung cancers, it is fast becoming a standard for most other cancers. MR and MR spectrometry are other imaging modalities that could potentially be fused with molecular PET techniques.[8]

Many other newer techniques such as magnetic resonance spectroscopy, impedance tomography, and laser optical tomography are increasingly being studied for application to cancer imaging.[6]

4. Cancer therapy

Surgery, radiation and chemotherapy are the oldest treatment modalities for malignancies. From the time cancer is first suspected or diagnosed, there is need for the different cancer disciplines to work together to formulate the best treatment plan for the patient. Since each patient and each cancer is different, treatment must be individualized. The exact treatment choice or combination of choices will depend on the patient, the disease and the stage of the disease as well as other considerations such as performance status, and comorbid conditions.

4.1 Pharmacotherapy

Cytotoxic agents still form the basis of many cancer therapy regimens. The growth pattern of individual neoplastic cells may greatly affect the overall behavior of tumors and their responses to specific types of cancer therapy.

The cell cycle gives us an insight into the kinetic behavior of dividing cells.[9] The four distinct phases of the cell cycle are: G_1, G_2 ,S and M phases. G_1 is a stage of cell increase or growth. This is followed by DNA replication or synthesis during the S (*synthesis*) phase. G_2 is another stage of cell growth. During the M (*mitosis*) stage, the cell growth is halted while active division takes place. During the G_1 and G_2 phases, the cellular constituents are synthesized. The cell cycle is well regulated with checkpoints that ensure that cells moved into the next cell cycle phase only after the proceeding phases are well completed. These checkpoints may become abnormal in cancer.

Some cytotoxics act at specific points in the cell cycle. Antimetabolites are more active against the S-phase cells while the vinca alkaloids and taxols are more M-phase specific.

Alkylating agents and platinum derivatives are cell-cycle-nonspecific agents. **Fig 1** and **Table 2** list some chemotherapeutic agents in common use and their mechanisms of action.

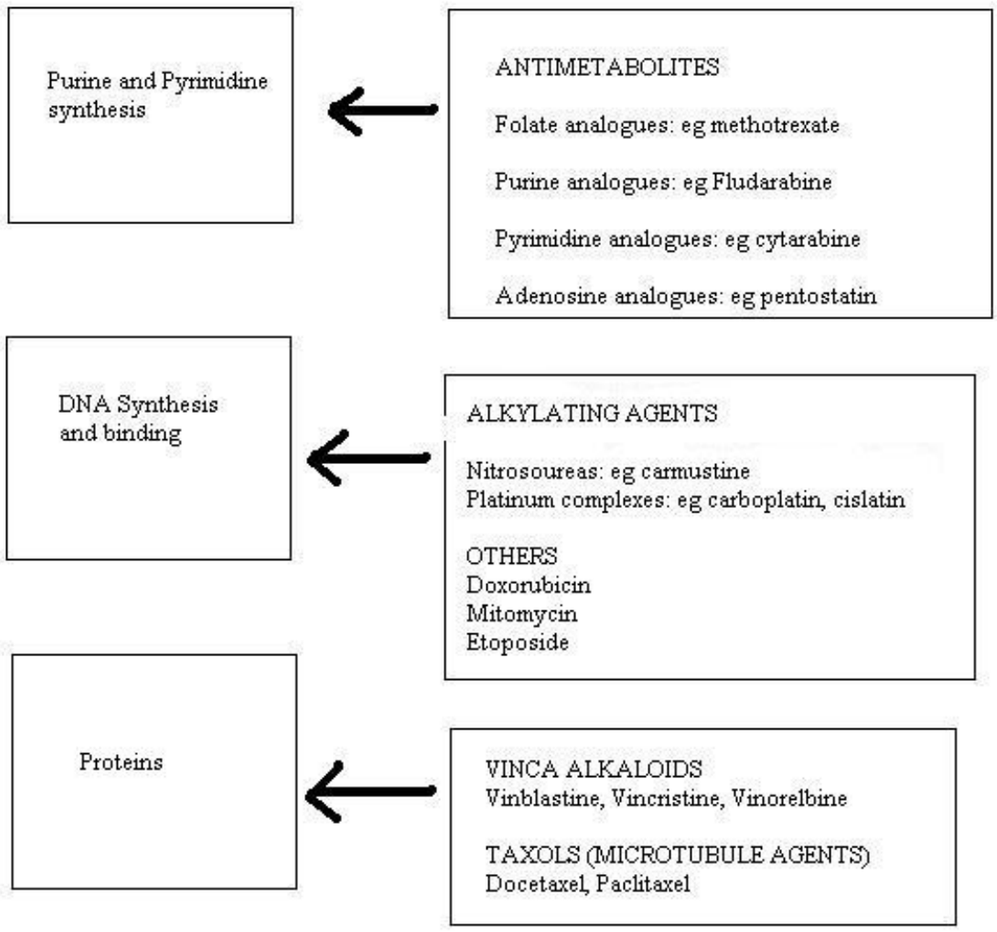

Fig. 1. Action of selected chemotherapeutic agent.

Chemotherapeutic agents are used as primary treatment for advanced disease, as neoadjucant to surgery/ radiation for localized disease or as adjuvant therapy (with surgery and/or radiation). In addition to systemic administration, anticancer agents can also be delivered regionally. Classical examples of regional delivery of chemotherapy include intrathecal administration of methothrexate in the treatment and prevention of meningeal leukemia, intraperitoneal chemotherapy in management of ovarian cancer, intravesical treatment for superficial bladder cancer, and intrahepatic arterial therapy for colon cancer metastatic to the liver.[10]

4.2 Target cancer therapies

Recent advances in genetics and molecular cellular biology has led to exponential increase in our understanding of the molecular events that either initiate or sustain cancer growth. Whereas traditional chemotherapeutic agents may not differentiate between normal and cancer cells, the newer biological agents target specific molecular pathology (pathways and

aberrant genes)in cancer cells.[11] Target therapeutics can be monoclonal antibodies or small molecules. They can be used alone or in combination with other chemotherapeutics, surgery or radiation therapy.

4.3 Monoclonal antibodies

Monoclonal antibodies are antibodies that bind to antigens found specifically on cancer cells and thus induce an immune reaction against the cancer cells. These antigens are usually extra-cellular proteins or cell surface antigens that are expressed specifically by the neoplastic cells.

Many monoclonal antibodies have been produced and find use in treatment of autoimmune and oncological disorders. Their names usually end in the letters –*mab*-short for monoclonal antibodies**.(Table 3)** Some antibodies are already approved for clinical use whereas many others are still experimental and undergoing clinical trials.

4.4 Small molecules

By virtue of their size, small molecules can reach intracellular sites where they act to interact with molecular pathways and exert anti-tumor effects. **Table 4** enumerates some of the small molecules that are currently in clinical use.

4.5 Endocrine therapy

Use of hormones in Oncology is based on the recognition that some human cancers undergo changes following fluctuations in certain sex hormones. Hormone deprivation can be achieved by surgical removal of the steroid gland or by administration of inhibitors of the hormone biosynthesis. Examples of hormonal therapy for cancers include use of antiestrogens and LHRH analogues for breast cancer as well as use of antiandrogens and LHRH analogues for prostate cancer. Steroids (prednisone, dexamethasone) are used either alone or in combination with other cytotoxic agents for the treatment of leukemias, lymphomas and multiple myelomas. Steroids are also used in the management of hypercalcemia as well as for the tissue swelling that accompanied tumors of the lungs and the airway obstruction.

Alkylating agents Bendamustine, cyclophospham, chlorambucil, ifosfamide, carmustine, lomustine, streptozocin, carboplastin, cisplatin, oxaliplatin, procarbazine, melphalan, busulphan, thiotepa *Antimetabolites* Methotrexate, pemetrexed, fludarabine, mercaptopurine, thioguanine, cladribine, pentostatin, capecitabine, cytarabine, floxuridinefluorouracil, gemcitabine, hydroxyurea *Natural products* Bleomycin, dactinomycin, daunorubicin, doxorubicin, doxil, epirubicin, idarubicin, mitomycin, etoposide, teniposide, docetaxel, paclitaxel, vinblastine, vincristine, vinorelbine, irinotecan, topotecan, asparaginase

Table 2. Chemotherapeutic agents

4.6 Radiation therapy

Radiation therapy is the administration of ionizing radiation to a cancer patient for the purpose of cure, palliation or as an adjunct to surgical treatment. Confirmation of malignancy by pathological exam, ancillary workup and staging must be completed prior to radiation therapy.

Radiation therapy is often used in conjunction with surgery for eradication of small, limited human cancers. Preoperatively, radiation therapy may be given to shrink inoperable tumors or to destroy unrecognized peripheral projections of the tumor. This method is applicable to advanced tumors of the head and neck, colorectum and bladder. On the other hand, radiation therapy can be given post operatively to eradicate residual disease or to control subclinical disease in the wound or in the lymphnodes.[12]

Radiation therapy is also used for palliation in instances like cancers of the central nervous system and pathological metastasis to the bones

4.7 Surgery

Surgery plays vital role in the prevention, diagnosis, staging, cure and palliation. Many premalignant lesions are usually surgically removed to prevent progression to cancer. Family members with familial polyposis of the colon for example, are routinely being offered colectomy to prevent eventual development of colon cancer. Mastectomy can also be done prophylactically for patients at high risk for breast cancer following the appropriate genetic counseling.

Incisional, excisional and needle biopsy techniques as well as endoscopy are surgical methods that aid cancer diagnosis.

Surgery forms the basis of therapy for early cancer in which case it is employed as local treatment for small tumors, to reduce the bulk of the disease, and for removal of metastatic tumors.

Even though late stage cancers are mainly treated by chemotherapy, surgery could offer palliation in advanced cancers. Typical examples of such instances include stenting for biliary obstruction due to advanced tumors of the biliary system or for esophageal obstruction.

4.8 Gene therapy

Cancer gene therapy is anchored on the premise that many cancers are due to genetic alterations that eventually lead to malignant changes in tissues. Gene therapy involves the transfer of genetic material into a cell to alter the cellular phenotype transiently or permanently. Gene transfer can be performed in vitro or in vivo. Different vectors exist for gene delivery into cancerous cells. Viruses (such as retroviruses) serve as a perfect tool for gene transfer. Gene therapies for cancer treatment are evolving and are largely still undergoing studies.

5. Conclusion

The general practitioner will see cancer patients at one time or the other in the course of their disease. Even though the primary care practitioner is not a medical, surgical or radio-

oncologist, he is part of the interdisciplinary team that is crucial for provision of optimal care for the cancer patient or cancer survivor. Burdened with such a responsibility, the general practitioner must keep abreast of the available screening, diagnostic and therapeutic modalities that currently exist for malignant diseases. Surgery, radiation and chemotherapy still play a large role in the treatment of cancer. But with advances in molecular biology and individualized medicine, many new diagnostic and treatment options are gradually shifting towards identifying and treating cancer at the level of the genes or molecular pathways. The

Agent	**Molecular target**	**Disease indication**
Trastuzumab(Herceptin)	ERBB2	Breast cancer
Bevacizumab(Avastin)	VEGFR	Metastatic colorectal cancer
Cetuximab (Erbitux)	EGFR	Metastatic colorectal cancer
Alemtuzumab(Campath)	CD52	B-cell Chronic lymphocytic leukemia

Table 3. Examples of monoclonal antibodies

Drug	**Molecular target**	**Uses/Disease indication**
Bortezomib	26S proteosome	Multiple myeloma
Dasatinib	brc-abl,PDGFR	CML, Philadelphia positiveALL
Erlotinib	HER1/EGFR	NCSLC ,pancreas
Gefitinib	EGFR	NSCLC
Imatinib	brc-abl,PDGFR	CML,GIST
Lapatinib	EGFR,HER2	HER-2 positive metastatic breast cancer
Nilotinib	brc-abl,PDGFR	CML
Sorafenib	VEGFR,PDGFR,RAF-1	renal cell cancer
Sunitinib	VEGFR,PDGFR,RET,c-kit	renal cell cancer, GIST
Temsirolimus	mTOR	renal cell cancer

Modified from *Cancer management: A multidisciplinary approach*. 11th ed. Lawrence,Kansas: CMPMedica.

Table 4. Targeted cancer therapeutics: small molecules

primary care provider will therefore increasingly encounter patients that are being treated with these new cancer therapies. Stem cell and genetic therapies as well as some target therapies are still evolving and over the next few years will find their way into our therapeutic regimens.

6. Abbreviations

ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
BTA	bladder tumor antigen
CML	chronic myelogenous leukemia
CT	computed tomography
BCR-ABL	oncogene fusion protein associated with the Philadelphia chromosome
EGFR	epidermal growth factor receptor
HER2-NEU	human epidermal growth factor receptor 2
DNA	deoxyribonucleic acid
FISH	fluorescence in situ hybridization
GIST	gastrointestinal stromal tumor
IHC	immunohistochemistry
MRI	magnetic resonance imaging
PET	positron emission tomography
PET-CT	positron emission tomography-computed tomography
VEGFR	vascular endothelial growth factor receptor

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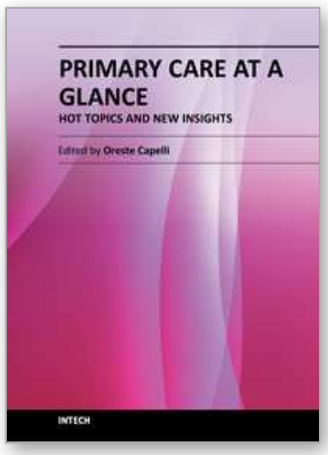

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"Both among scientists and clinical practitioners, some find it easier to rely upon trivial explanations, while others never stop looking for answers". With these surprising words, Augusto Murri, an Italian master in clinical medicine, reminds us that medical practice should be a continuous journey towards knowledge and the quality of care. The book brings together contributions by over 50 authors from many countries, all around the world, from Europe to Africa, from Asia to Australia, from North to South America. Different cultures are presented together, from those with advanced technologies to those of intangible spirituality, but they are all connected by five professional attributes, that in the 1978 the Institute of Medicine (IOM)1 stated as essentials of practicing good Primary Care: accessibility, comprehensiveness, coordination, continuity and accountability. The content of the book is organized according to these 5 attributes, to give the reader an international overview of hot topics and new insights in Primary Care, all around the world.

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