INFORMETRIC APPROACHES OF COLORECTAL CANCER

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Submitted by

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1. Thesis title: INFORMETRIC APPROACHES OF COLORECTAL CANCER.
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6. The report has been prepared without resorting to plagiarism.
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ABSTRACT

Colorectal cancer is the world's third most common form of cancer and a significant cause of death from cancer. To obtain a cure for colorectal cancer, early diagnosis and screening is necessary as well as clear understanding of molecular basis of disease. Molecular characterization of mutations associated with cancer provide useful information on the prognosis and the reaction to therapy. This review discusses about clinical, molecular and pathogenic feature of early onset of CRC and its screening test and diagnosis. The recent advances and rapid growth of computational tools in colorectal cancer diagnosis as well as screening, which include AI, CAD, molecular docking, machine learning and deep learning etc. are outlined. In recent developments application of artificial intelligence has proved its excellency and shown a promising result, pointing out the severe need for multidisciplinary approach to achieve the excellent result.

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List of Symbols, Abbreviations and Nomenclature

α- alpha

β- beta

CRC- Colorectal cancer

AI- Artificial Intelligence

CAD- Computer aided diagnosis

MMR- mismatch repair

MSI- microsatellite instability

PI3K- phosphatidylinositol 3-kinase

TGF- transformation growth factor

c-MYC- Cellular Myelocytomatosis

LEF- lymphoid enhancer factor

CK1- casein kinase1

APC- Adenomatous polyposis coli

GSK3- glycogen synthase kinase3

NF-κB- nuclear factor kappa-light-chain-enhancer of activated B cells

CNN- coevolutionary neural network

SVM- support vector machine

1. Introduction

Colorectal cancer (CRC) ranks as the second most lethal & highest mortality rate cancer and the third most prevalent malignant tumour across the world. There were 1.8 million new CRC cases, & there were 881,000 deaths recorded in 2018, which consider for almost 10 percent of new cases of cancer and death globally, and the number of new cases could be rise to almost 25 lakhs in 2035(Siegel et al.,2020). It is a disease in which irregular growth is found in the cells of the colon or rectum. The cancers are predominantly adenocarcinoma. Colorectal cancer starts with polyp outgrowth, which grows on the inner wall of the rectum or colon & after sometime these polyps can become life threatening tumour. By perceiving till eliminating the polyps in the beginning phases, colorectal tumor might be kept away from and its screening has been demonstrated to significantly diminish mortality and in certain cases, may prevent the beginning of sickness through the evacuation of precancerous polyps(Center et al., 2009). Generally the best CRC treatment is to accomplish total expulsion of the neoplasm and metastasis, which generally requires surgery. Despite the rise of various screening projects to decline the colorectal cancer occurrence, almost a quarter cases of CRCs are recognized at a high-level stage with metastases, and 20% of the remaining cases are probably going to create metachronous metastases, which make surgery control challenging and lead to tumour-related deaths(Saika et al.,2013).

CRC is a biologically and molecularly heterogeneous category of disorders in which various patterns of mutations are responsible for the disease's onset and progression, as well as its aggressiveness and response to therapy(DE ROSA et al., 2015). Molecular characterization of mutations associated with cancer provides useful information on the prognosis and reaction of the disease to therapy. To obtain a cure for CRC, speedily detection and management, as well as a clearer understanding of the molecular basis of the disease's initiation and progression, are also essential. According to recent studies, colorectal cancer can be relieved of much of the pain and discomfort associated with it, as well as reduce the number of deaths caused by the disease, with adequate screening and care. Early management of extreme atypical hyperplasia or CRC has been shown in comparative studies to improve overall survival(Atkin et al., 2010; Schoen et al., 2012; Singh et al., 2010). Furthermore, unfinished biopsy often leads to the diagnosis error of early CRC as mild or moderate abnormality, resulting in ineffective treatment(Bick et al., 2016; Edge & Compton, 2010; Hermans et al., 2018; Neerincx et al., 2010). Since the TNM stage is one of the best predictors of CRC(Fleming et al.,2012), statistics particular to the stage primarily therapy. Recent study demonstrated that detecting and removing colorectal polyps can help to prevent adenocarcinoma from developing, as well as that detecting and treating cancers in their early stages can reduce mortality

rates(*American Cancer Society | Information and Resources about for Cancer: Breast, Colon, Lung, Prostate, Skin*, 2020; Newcomb et al., 1992).Narrow-band imaging (NBI) or other techniques like I-scan or Fujinon intelligent chromoendoscopy (FICE) have almost completely substitute standard chromoendoscopy. Virtual chromoendoscopy is easy to use, fast to set up, and can be switched on and off during the operation. It is also widely available(Fleming et al.,2012).Deep learning models have also been shown to help endoscopists diagnose polyps or adenoma(Chen et al., 2018; Misawa et al., 2018)as well as upper gastrointestinal cancer(Luo et al.,2019).

By the age of 65, up to 75% of patients inherited with nonpolyposis colorectal cancer experience malignant disease. Germ line mutations in MMR genes cause this autosomal dominant syndrome. Gene involving in CRC are mentioned in table 1(Ballester et al.,2016;Kastrinos et al.,2011; Vasen et al., 1991) Poor compliance is a major disadvantage of faecal occult blood testing as a screening method. In large trials, only 38 to 60% of patients completed all expected experiments(Kronborg et al .,1996). MSI is linked with many cancer subtypes and assist in guiding therapeutic conclusion, so precise detection of MSI in cancer cells is critical. While experimental assays for detecting MSI have been established, their reliability is restricted because they usually rely on a few numbers of known microsatellite loci or MMR genes(Lu et al., 2013).

Table 1: Genes present in inherited syndrome of cancer.

GENES INVOLVED IN HEREDITARY COLORECTAL CANCER SYNDROME

SYNDROME	GENE	HEREDITARY
Hereditary Non-Polyposis Colorectal Cancer (HNPCC)	MLH1, MSH2, MSH6, MLH3 , MSH3 AND PMS2	Dominant
Polymerase Proofreading – Associated Polyposis (PPAP)	POLD1 – POLE	Dominant
Familial Adenomatous Polyposis (FAP)	APC Gene	Dominant
Attenuated Familial Adenomatous Polyposis (AFAP)	APC Gene	Dominant
MUTYH – Associated Polyposis (MAP)	MUTYH	Dominant
Peutz – Jeghers Syndrome (PJS)	STK11/LKB1	Dominant
PTEN Hamartoma Tumors Syndrome (PHTS)	PTEN	Dominant

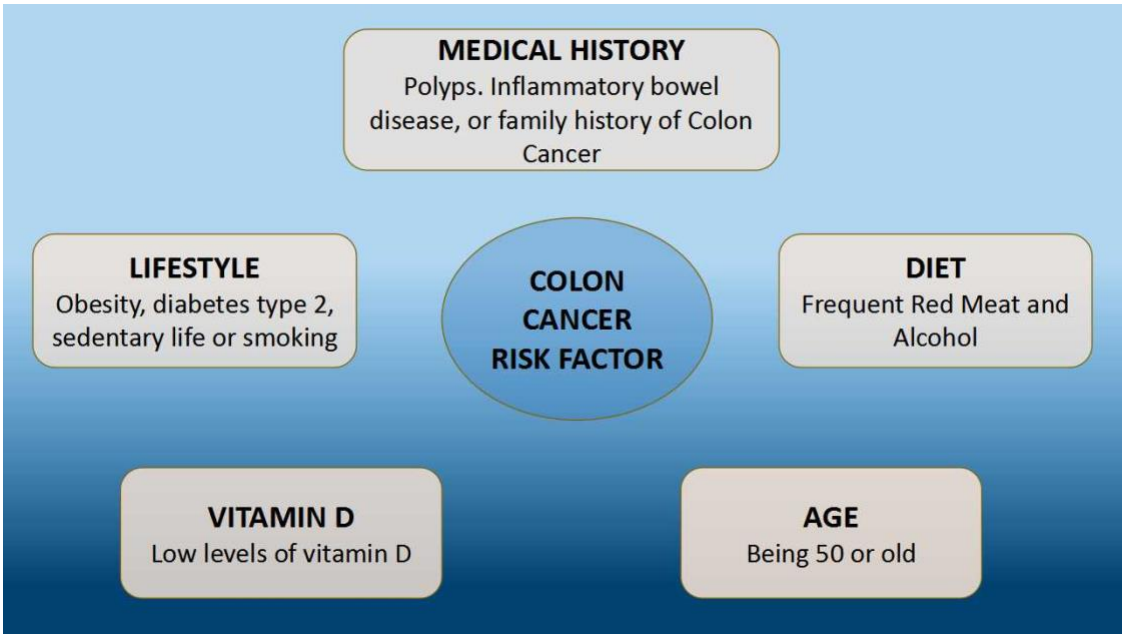


Figure 1:Various risk factor present in colorectal cancer

2. Clinical, pathological and molecular feature of early onset of CRC

Epithelial cells from the gastrointestinal tract gain concurrent genetic and epigenetic mutations in particular oncogenes and/or tumor suppressor genes in the development of colorectal adenocarcinoma, providing them a significant benefit in proliferation and self-renewal. As a result, normal epithelium develops into a hyperproliferative mucosa, which then develops into a benign adenoma that develops into carcinoma and spreads in ten years. Somatic mutations account for aapprox. seventy % of all colorectal cancer(Lech et al.,2016).

There are three forms of pathogenic pathways: chromosomal instability (CIN), microsatellite instability (MSI), and CpG island methylator phenotype (CIMP).

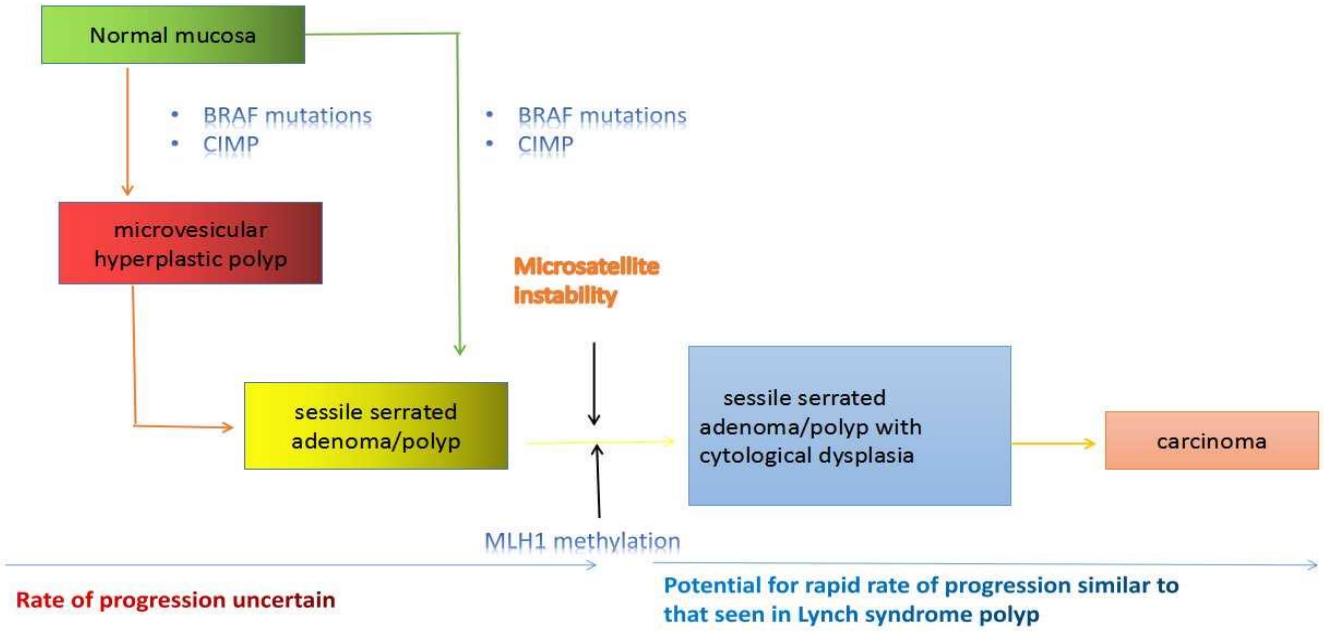


Figure2: schematic representation of CIMP along with MSI through serrated pathway.

common mutations, chromosomal modifications, and translocations have been identified to change main pathways (WNT, MAPK/PI3K, TGF-, TP53), and mutations in, genes like c-MYC, KRAS, BRAF, PIK3CA, PTEN, SMAD2 and SMAD4 can be used as predictive markers for patient outcome in these types of CRC(Ahmed et al., 2014; Al-Sohaily et al., 2012). Microsatellite instability (MSI), a hypermutable phenotype, results from the failure of DNA mismatch repair. MSI is present in 15% of colorectal cancers, with MSI being linked lynch syndrome to 3% of these cancers as well as 12% is brought by Hypermethylation of the MLH1 gene promoter, which occurs in tumors with the CpG islands methylator phenotype as shown in figure3(Lam, 2014)

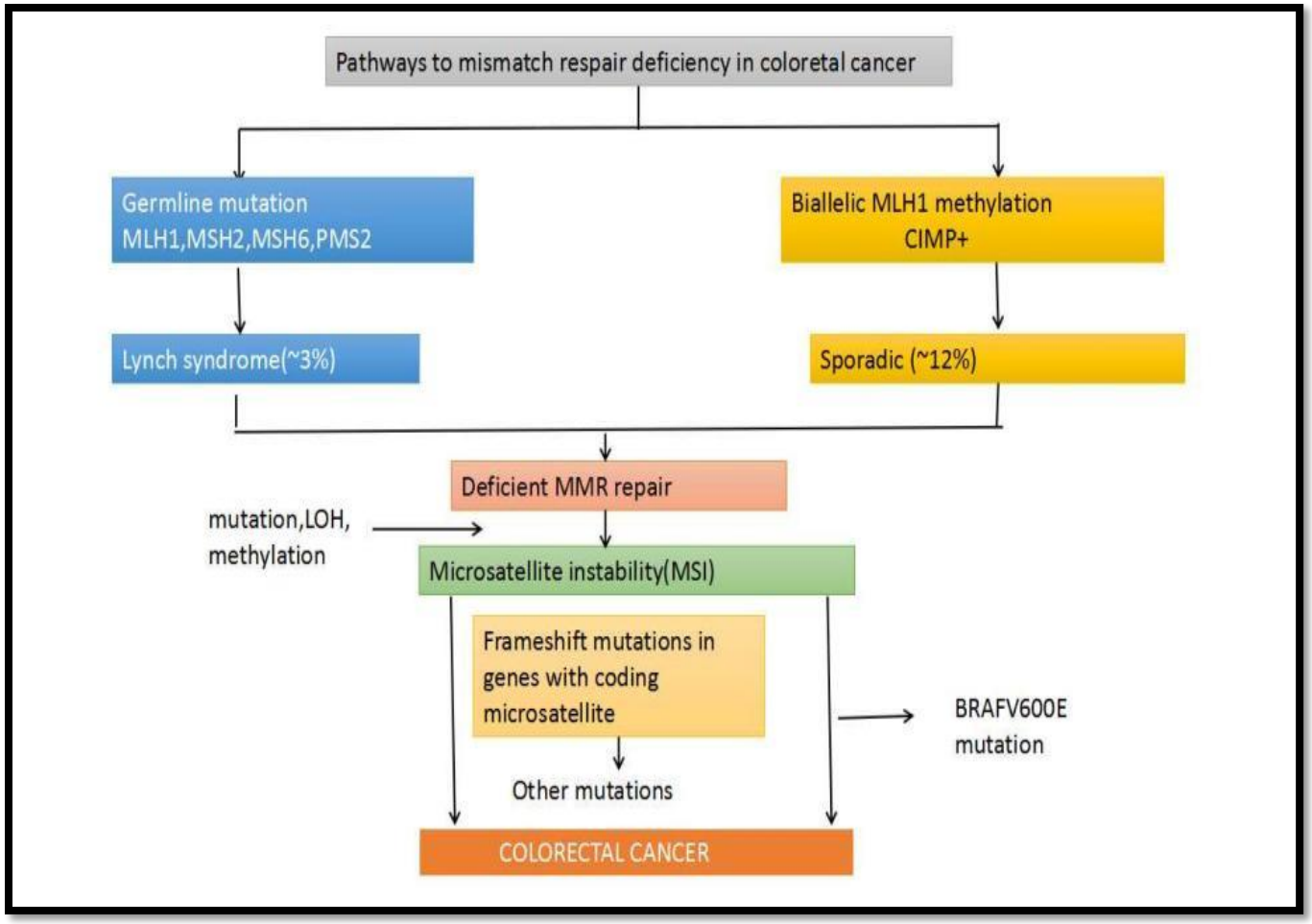


Figure3: MSI causing colorectal cancer through two different molecular pathways.

The majority of synchronous colorectal carcinoma in molecular biology research has concentrated on the study of microsatellite instability (MSI)(Hu et al., 2013). MSI predicts 5-fluorouracil response negatively and can also be used to determine resistance to other medications used to treat colorectal cancer. More molecular heterogeneity has been discovered in MSI tumors recently, which could help us better understand differential chemosensitivity(Pin et al., 2011). Microsatellite instability testing by PCR, BRAF V600E mutation testing, and MLH1 promoter methylation testing all need dissection of the tumor from the paraffin-embedded sample. This is usually achieved by manually dissecting tissue from a particular part of the slide(Boland & Goel, 2010; Geiersbach & Samowitz, 2011; Sinicrope & Sargent, 2012).

Table2: Patterns of genomic instability in colorectal cancer.

TYPES OF INSTABILITY	TYPES OF DEFECT	PHENOTYPE
• MICROSATELITE INSTABILITY (MIN)	• GERMLINE	• Multiple primary colorectal cancers, accelerated tumor progression, and increased risk of endometrial, gastric, and urothelial tumors.
• CHROMOSOMAL INSTABLITY (CIM)	• SOMATIC	• Characteristic of 80-85% sporadic colorectal cancers, depending on stage.
• CpG ISLAND METHYLATOR PHENOTYPE (CIMP)	• SOMATIC	• Characteristic of 15% of colorectal cancers, with most showing mismatch repair deficiency from loss of tumor MLH1 expression.

Several modified molecular signalling pathways, such as Wnt/APC/β-catenin,(PI3K)/AKT/(GSK-3β), (TGF)-β/Smad, NF- βb or MMR genes, are all involved in CRC onset (MMR). Individual cancer sensitivity is determined by such modification which are also responsible for anti-tumor agent responsiveness or resistance.

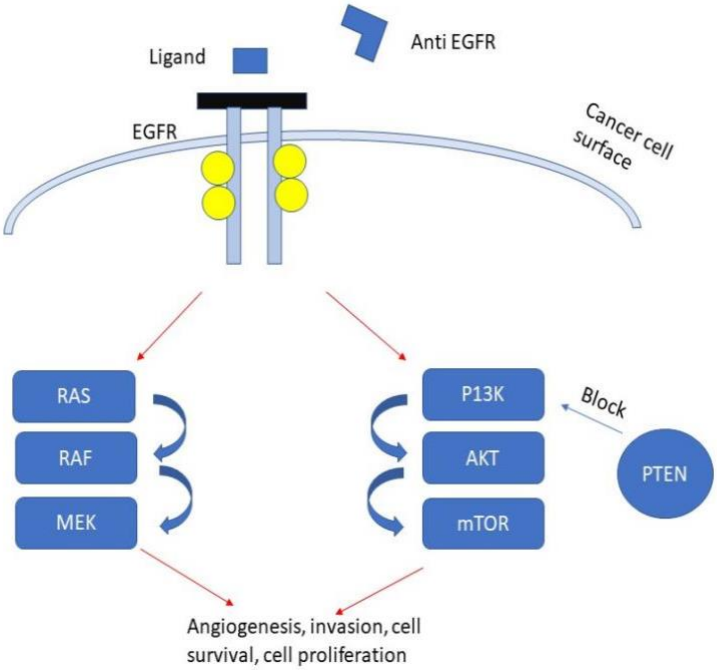


Figure4- The EGFR pathway and its downstream effectors, PI3K/AKT and KRAS/BRAF/MEK/MERK, are discussed.

2.1 Wnt/β-catenin pathway

Sporadic CRC, is the more usually unstable signal pathway. When Wnt ligand which is a secreted glycoprotein, gets binds to its Frizzled (Fz) receptors, the multifunctional kinase GSK-3 and β-catenin, is deactivated, which serves as an E-cadherin cell-cell adhesion protein as well as transcriptional activator, which is stabilized, gathered in the cytoplasm, and ultimately translocated into the nucleus, in which it interacts with lymphoid enhancer factor (LEF)/t-cell factor (TCF) as shown in figure5. In lack of Wnt signaling, β-catenin phosphorylate for ubiquitination and proteasomal degradation by casein kinase1 (CK1) and the APC/Axin/GSK-3 complex, thus preventing their nuclear translocation(Geiersbach & Samowitz, 2011; Giles et al., 2003; MacDonald et al., 2009; Polakis et al., 2000)

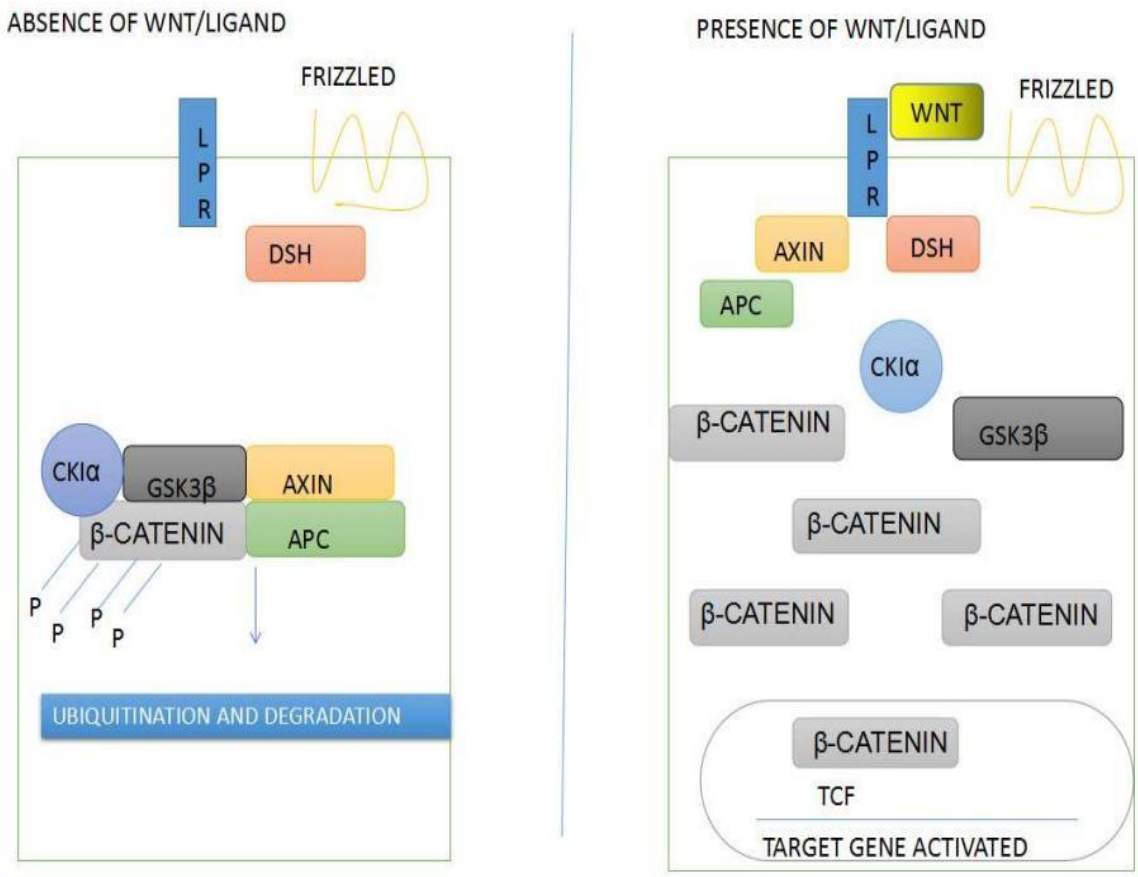


Figure5: Wnt/ beta-catenin pathway

2.2 PI3K/AKT pathways

The PI3K/AKT/PTEN pathway, which is quite found non functional in the matching erratic as well as inherited colorectal which promotes cell growth and inhibits apoptosis in reaction to many exogenous stimuli like cytokines, hypoxia, growth factors, heat , hormones, oxidative stress, and hypoglycaemia.In several cellular proceding, like metabolic regulation, apoptosis, the cell cycle, translation AKT works by phosphorylating many specific proteins, such as β-cateninin, caspase-9, mTOR , BAD and GSK3(Martini et al., 2014; Shaw & Cantley, 2006).

2.3 Ras/Raf pathway

Ras/Raf signaling control the activation of mitogen-activated protein kinase, a bunch of serine/threonine kinase proteins which directs signal transduction from the plasma membrane to the nucleus, in reaction to various external stimuli like mitogenic factors and growth. The Ras genes which found on chromosome 12 as well as encode small proteins that activate GTPases in the plasma membrane(Hallberg et al., 1994; Malumbres & Barbacid, 2003).

2.4 NF-κB pathway

NF-kB is a cell proliferation and inflammation signaling pathway. It has 5 transcription factor subunits which are RelA/p65, c-Rel, RelB, p50/NF-κB1 and p52/NF-κB2, which can dimerize as well as segregate by Iκb proteins in the cytoplasm(Chen et al., 2018; Perkins, 2004).

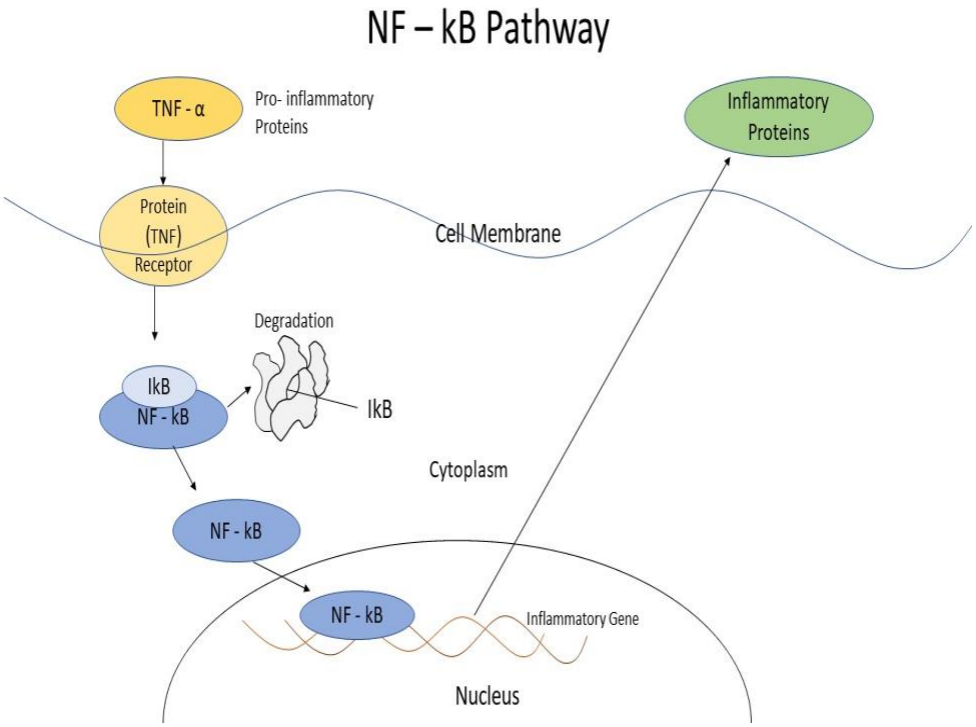


Figure6: NF-kB Pathway

2.5 Epithelial-to-mesenchymal transition (EMT) pathway

EMT is implied as a ordinary biological mechanism in molecular heterogeneity as well as in the treatment of cancer, representing a good therapeutic intervention target. It contains the critical phenotypic transformation of mesenchymal phenotype cells into epithelial cells. It is a reversal procedure that happen during embryonic growth and tissue remodeling, and it often applied a key role in the initial stages of invasion and metastasis in several form of cancer like CRC cancer(Loboda et al., 2011).

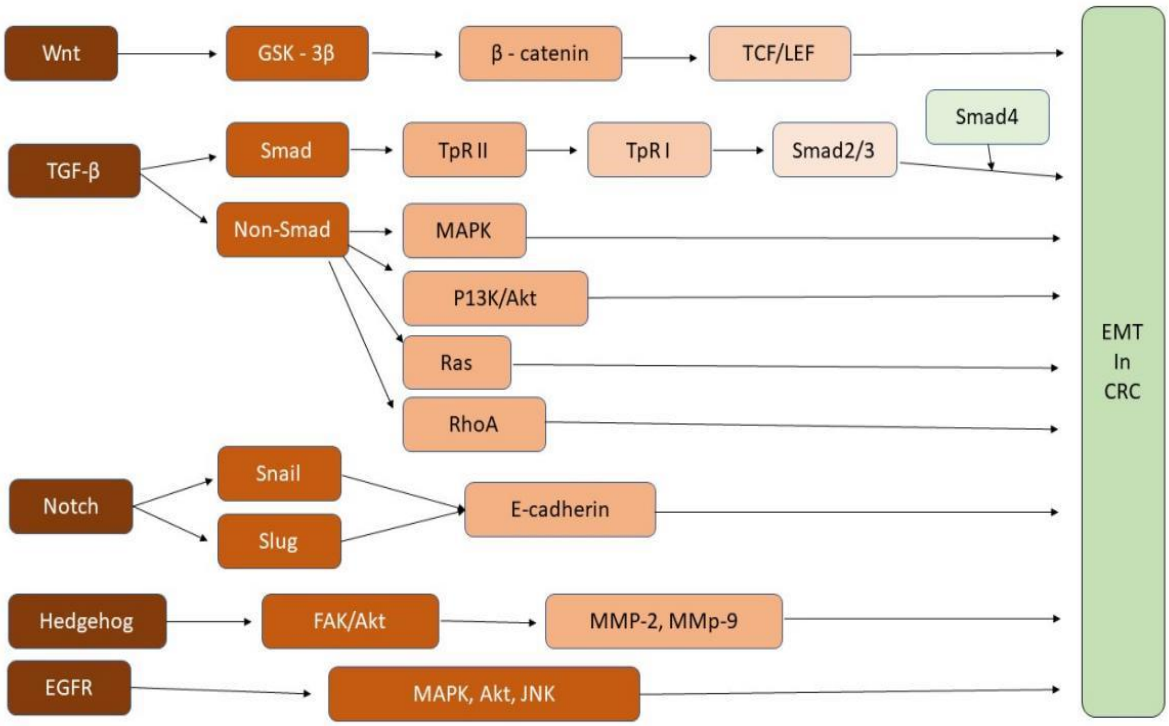


Figure7: EMT Pathway

3.Recent advances in colorectal cancer diagnosis and staging

The characteristics of colorectal cancer are determined by the position of the lesion clinically. Hematochezia may be caused by both right colon lesions and left colon lesions, but occult bleeding is more common, causing anemia and fatigue. Hematochezia, bleeding, or tenesmus are caused by rectal lesions. Up to thirty percent of colorectal carcinoma patient are predominantly diagnosed with sub/obstructing symptoms in an acute stage. In order to exclude synchronous lesions or distant metastases, patients with newly diagnosed CRC need full staging work. Tumors of distal extension to approximately 15 cm (as measured by Rigid sigmoidoscopy is categorized as rectal from the anal margin and more proximal tumors are classified as colon cancer(Mármol et al., 2017).

To ensure a proper treatment plan, accurate diagnosis and staging are required. The mortality chances of colorectal cancer has reduced by more than twenty percent in the past ten years due to improvements in diagnostic procedure & enhancement of surgical, adjuvant, and palliative therapies. The number of biomarkers used in studies is steadily increasing. The National Health Institute describe a biomarker as a biotic molecule found in blood, body fluids, or other tissues,which is indication of natural/an irregular process, or whether a disease or disorder exists .Colorectal cancers in the Stage 0 (a very early cancer) is

the first stage, followed by stages1-4 .In general, less the number implies that the less cancer has spread. A greater number suggests that the cancer has developed to a next stage, such as stage IV. A lower level is indicated by an earlier letter within a phase.

TABLE3: Stages of cancer with its description.

STAGES	TNM STAGE	STAGE DESCRIPTION
STAGE 0	Tis N0 M0	Tis- cancer in situ; tumor cells are confined to mucosa/ inner lining
STAGE 1	T1 N0 M0 T2 N0 M0	T1- tumor invades the submucosa T2- tumor invades into muscularis propria
STAGE 2A	T3 N0 M0	T3- tumor invades submucosa
STAGE 2B	T4 N0 M0	T4- tumor invades adjacent organs
STAGE 3A	T1-2 N1 M0	N1-metastasis to 1-3 regional lymph nodes, and T1/T2
STAGE 3B	T3-4 N1 M0	N1- metastasis to 3-4 regional lymph nodes , T3/T4
STAGE 3C	ANY T N2 M0	N2- metastasis to 4 regional lymph node, any T
STAGE 4	ANY T ANY N M1	M1-distant metastases present, any T any N

3.1 Screening test

Colorectal cancer screening includes checking for precancerous colorectal polyps or early-stage cancer before signs occur, before the disease has a chance to develop or spread, and thus treatment is easier to administer, less costly and more likely to succeed.(Marley et al., 2016). Typically, noncancerous polyp is started growing slowly in colorectal cancer which further develop into invasive cancer over time. If a cancerous polyp may penetrate the lining of the large intestine if it is not removed which further, allows the cancer to transfer to other organs via blood / lymph vessels(Worthley et al.,2010).

Recommended by several guidelines, Stool-based tests for advance-stage colorectal cancer and endoscopic tests, such as flexible sigmoidoscopy and colonoscopy, to identify and eradicate pre-cancerous lesions/polyps, are among the detection methods(Bishehsari, 2014). Colorectal cancer can often be prevented through regular screening, which can find polyps before they become cancerous(Markowitz & Bertagnolli, 2009). These tests include:-

Table:4 various screening test with their advantages and disadvantages

SCREENING METHOD	FREQUENCY	ADVANTGES	DISADVANTAGES
STOOL BASED TEST • GUAIAC-BASED FECAL OCCULTT BLOOD TEST (gFOBT)	EVERY YEAR	NON-INVASIVE AND INEXPENSIVE	• LOW SENSITIVITY FOR POLYP • RELATIVELY LOW SPECIFICITY FOR CANCER
• IMMUNOCHEMICAL BASED FECAL OCCULT BLOOD TEST (iFOBT) OR FECAL IMMUNOCHEMICAL TEST(FIT)	EVERY YEAR	INCREASED SENSITIVITY WITHOUT LOSS OF SPECIFITY	• MORE EXPENSIVE THAN gFOBT • REQUIRE COMPLIANCE WITH ANNUAL TESTING AND COLONOSCOPY FOR POSITIVE RESULT
ENDOSCOPIC AND RADIOLOGIC EXAMINATION • FLEXIBLE SIGMOIDOSCOPY	EVERY 5 YEAR	• HIGH SENSITIVITY AND SPECIFICITY FOR DISTAL COLON • CAN BE PERFORMED WITH MINIMAL BOWEL PREPARATION • DOES NOT REQUIRE SEDATION	• ONLY IDENTIFY LESIONS IN THE DISTAL 60CM OF THE BOWEL. • ABNORMAL FINDINGS IN THE DISTAL BOWED MAY REQUIRE COLONOSCOPY
• COMPUTED TOMOGRAPHIC COLONOGRAPHY	EVERY 5 YEAR	• HIGH SENSITIVITY AND SPECIFICITY • DOES NOT RISK BOWEL PERFORATION	• POSITIVE FINDINGS REQUIRE COLONOSCOPY FOLLOW UP • CUMULATIVE DOSE OF RADIATION MAY INCREASE CANCER RISK
• COLONOSCOPY	EVERY 10 YEAR	• HIGHER SENSITIVITY AND SPECIFICITY	• REQUIRES CONSIOUS SEDATIVE

3.2 Optical diagnosis for colorectal polyps

Another important clinical application is a diagnosis of malignant colonic polyps optically in which it is vital to identify early intrusive cancers and predict the extent of invasion in order to choose the best healing plan. Currently, For quality benchmarks, for diminutive polyps optical diagnosis, there are 7 major classification systems and 3 key society guidelines(Djinbachian et al., 2019)Narrow-band imaging histology (NBI), I-scan, or Fujinon Intelligent chromoendoscopy are examples of new colonoscopes with image enhancement capabilities which reflect the underlying histology, detail polyp vascular and surface patterns(McGill et al., 2014)The Narrow Band Imaging International Colorectal Endoscopic (NICE) classification using NBI is an example of the diagnosis of colorectal polyps endoscopically, which explains (Kaltenbach et al., 2015)the real-time difference of (type 1- 3) colorectal polyps, i.e. non-neoplastic, neoplastic, submucosal invasion respectively(Picot et al., 2017)

This optical diagnosis technique has the possibility to make screening colonoscopy more cost-effective and efficient(Hassan et al., 2010; Kessler et al., 2011) Endoscopists must first acquire the expertise and skills

to distinguish polyp histology, then reach and maintain high standards of efficiency in order to integrate optical diagnosis into clinical practice.

3.2.1 Autofluorences

For automated optical diagnosis of polyps using special instruments, new technologies using laser-induced fluorescent spectroscopy are developed. Through this method, a computer fuse into a single-use biopsy forceps which further release light and get assimilated by polyps and re-emitted to the instrument with a spectrum of emissions different to the tissue. This method then analyses adenomatous and non-adenomatous polyps in red and in green color respectively. Therefore, this process bypasses training criteria for optical diagnosis for endoscopists because no imaging interpretation is needed for the diagnosis(van der Vlugt et al., 2016)

4.Computational approaches

Computational models of the intestinal crypt epithelium have helped researchers to investigate the mechanisms of crypt homeostasis, which were previously unknown. If properly parametrized, several models in this vast array seem to be able to capture the crypt's basic behaviour, such as transit times or monoclonal conversion. Continued performance in mathematical and computational modeling would require active participation of the Experimenters: for putting a model's predictions to the test by providing precisely quantified parameters, and finally, converting the model's findings into additional experimental data inquiry(Kershaw et al., 2013)

Many programs have been evolved such as algorithm of differential gene expression in complex diseases by network-based analysis These programs uses PPI as an integrative network to classify subnetworks that are dysregulated integrally in the phenotype. It is possible to diagnose cancer, recognize subtypes that affect a large number of people, and by using the same treatment protocols, heal or atleast slow the development of cancer in a significant number of patients. As a result, one of the most pressing issues in recent research is to discover the genetic variations that are common to all cancer cells, across its subtypes(Erten et al., 2012).

Novel algorithms was developed for network-based differential gene expression analysis in multiple phenotype groups applications and as an appropriate application it concentrate on defining subnetworks that can distinguish various stages of human colorectal cancer according to Dukes' classification . Using publicly available colorectal cancer datasets with samples labeled with Dukes' four phases. It looks at the efficacy of the final algorithm. Cobalt, is functional in detecting the stages of colon cancer samples in identifying subnetwork(Dao et al., 2010).

4.1 Artificial intelligence

Artificial intelligence (AI) has done a vital progress in radiological and disease diagnosis through gross and microscopic imaging, and has shown excellent outcome in the medical field(Eddy, 1990). The use of AI combined with narrow band imaging to distinguish the pathology of diminutive polyps in real time resulted in high diagnostic precision. In addition, for real-time cellular diagnosis, the application of AI with endocytoscopy or confocal laser endomicroscopy was investigated and the diagnostic precision of some studies was compared to that of pathologists. By avoiding unnecessary procedures, we can expect a higher polyp detection rate with AI technology in reduced time and expense, resulting in improved colonoscopy performance. However, more prospective studies with reduced selection bias, consensus on uniform use, and regulatory approval are required for AI implementation in actual daily clinical practise(Thakur et al., 2020)Endoscopist uses AI which could include a "closer glance" to reduce the incidence of unnoticed polyps during a colonoscopy. Integrating colonoscopy with advanced endoscopic modalities including laser-induced fluorescence spectroscopy and magnifying chromoendoscopy may help in diagnose and characterize polyps more effectively(Goyal et al., 2020; Kim & Kim, 2020).

The application of AI in the healthcare system, due to the large amount of data, has increased rapidly. Various AI techniques have been used in medical imaging, including machine and deep learning and the convolutionary neural network (CNN), which have allowed doctors to reliably diagnose and assess effective care for diseases(Rasouli et al., 2020). The cancerous cell growths in the colon were found to be abnormal were detected by artificial intelligence. If it embraces stability in future research, an 86 %precision figure of the machine learning process may be an extraordinary step in serving human ailments. According to Dr. Mori, the major significant breakthrough with this approach is that AI allows real-time optical biopsy of colorectal polyps during colonoscopy, independent of the endoscopist’s skills. Scientists have attempted to estimate how artificial intelligence can be used to assess the health risks of cancer, and it can be considered a boon for healthcare practitioners to efficiently detect diseases so that patients can be given appropriate treatment(Sadiq, 2020).

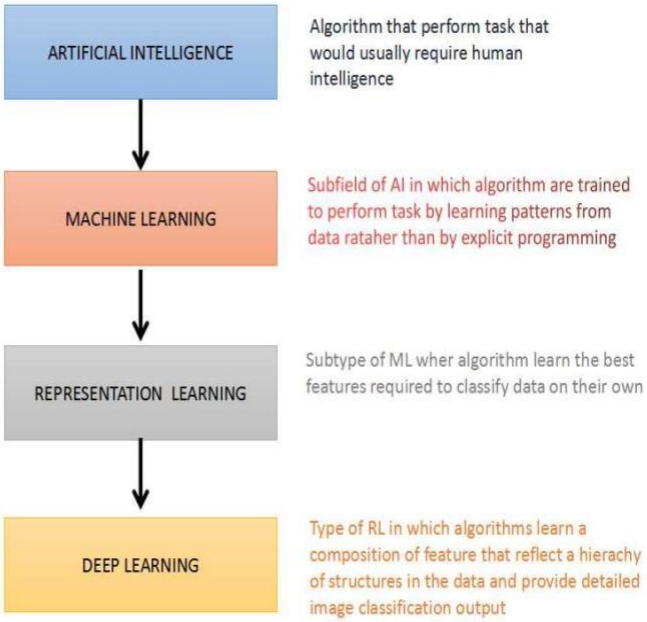


Figure 8: Hierarchy of artificial intelligence domains

4.1.1 AI in colorectal polyp histopathological recognition

The standard for diagnosing polyps is histopathological characterization of colorectal polyps. It's important for deciding whether patients may require potential endoscopic resection or routine follow-up. This characterization, however, is a difficult task with considerable intra- and inter-observer variability. It is important to develop an AI system that can assist pathologists in accurately identifying various types of colorectal polyps. Many scholars have begun to investigate this topic in recent years(Kainz et al., 2017; Korbar et al., 2017; Sena et al., 2019). *Korbar et al.* suggested artificial intelligence approach depend on deep neural network model which help in identifying about of colorectal polyps types on whole-slide,

hematoxylin, and eosin-stained images(Korbar et al., 2017).

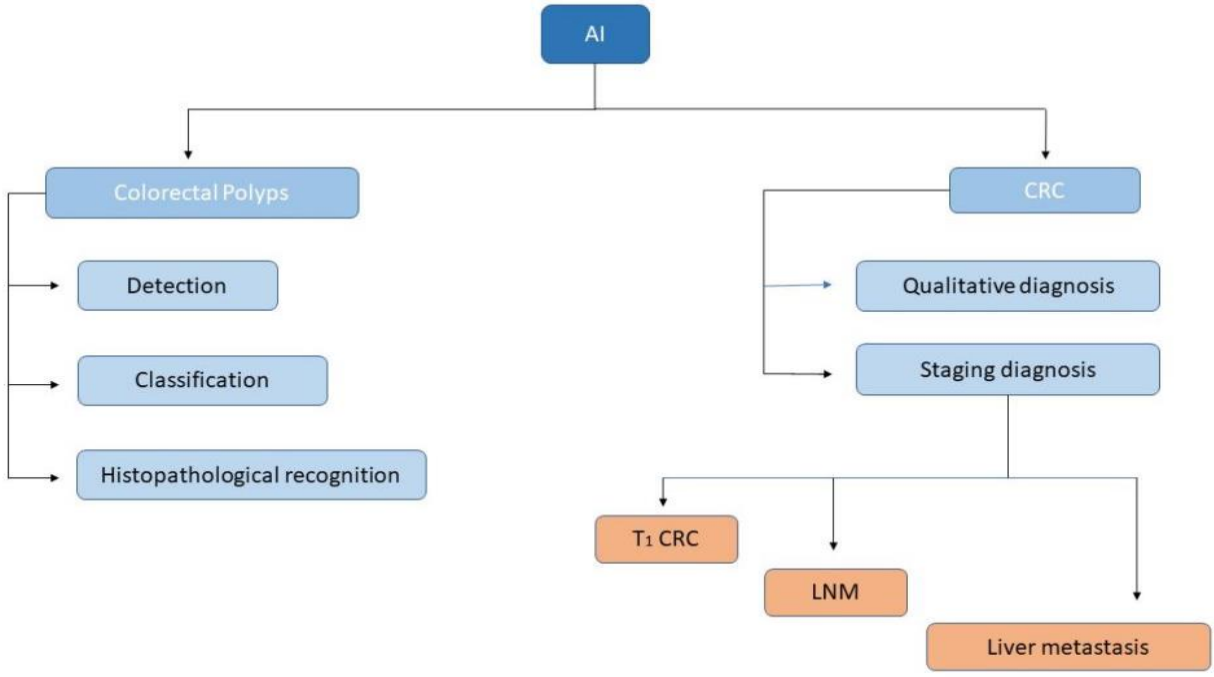


Figure9: AI in colorectal polyp and CRC.

4.1.2 AI in staging and qualitative diagnosis of CRC

Colorectal tumor diagnosis is divided into two categories: qualitative diagnosis and staging diagnosis. Colonoscopy and pathological biopsy are used in qualitative diagnosis to find out whether there are any colorectal tumors present. Colonoscopy has proved to be a successful tool for identifying cancerous lesions early on. The precision of magnifying endoscopy(Kudo et al., 1996), narrow-band imaging(Atkinson et al., 2019), endocytoscopy(Wang & Dong, 2020), and confocal laser endomicroscopy(De Palma et al., 2016) is higher, but the outcomes are operator based. It is hard to train all endoscopists to be proficient in all techniques. To resolve this problem, a CAD framework for endocytoscopy was developed. *Takeda et al.* conducted research to determine the treatment potential of a computer aided diagnosis device for endocytoscopy in the diagnosis of invasive colorectal cancer. In this research, a computer aided diagnosis method for endocytoscopy examine endocytoscopy images based on texture analysis and other data.AI is often used to assess the stage of a CRC. CRC is typically staged using CT, MRI, and other imaging techniques(Takeda et al., 2017).

4.1.3 AI and CRC monitoring and diagnosis

One of the fundamental principles of medicine is diagnosis, which is based on the integration of multi-source data analysis and clinician experience. It's difficult to make an accurate tumor diagnosis because of the wide range of tumor symptoms, the rapidity with which tumors progress, individual differences, and drug susceptibility.AI can help doctors with colon cancer diagnosis and staging, which currently rely on colonoscopy and pathological biopsy(Ahadova et al., 2020)

4.1.4 AI application in pathological biopsy

The diagnosis and grading of colon cancer require a pathological biopsy. However, pathologists' findings are usually subjective evaluations based on their previous experience and expertise. As a result, large differences between observers are unavoidable. (Rathore et al., 2015) developed a new colorectal cancer detection (CCD) framework based on the SVM radial basis function algorithm that classifies common and malignant colon biopsy visuals automatically and calculates malignant grades(Acs et al., 2020)

4.1.5 AI application during colonoscopy

Colonoscopy can be used to directly observe lesions in the intestinal wall, and colonoscopy doctors can use image analysis and screening to assess whether lesions are associated to CRC. Lefere first proposed the concept of virtual colonoscopy in 2006(Lefere et al., 2006). Virtual colonoscopy was first introduced in 1994 with computed tomography colonography(Halligan et al., 2005), which converted local axial computed tomography images into three-dimensional cavity images. These images used different types of films or virtual crosses to detect CRC and their adenomatoid polypoid precursors, as well as other neoplastic lesions, simulating optical colonoscopy. Colonoscopy has become a convenient and precise examination for screening CRC due to the rapid development of AI technology in recent years. (Fernández-Esparrach et al., 2016)developed an energy maps to detect polyps by automated colonic polyp detection technique.

4.1.6 Application of AI to CRC

Since 2010, there has been a substantial increase in AI research and application in medically assisted gastrointestinal disease diagnosis and treatment(Min et al., 2019). AI has aided in the examination of colorectal disorders, including colon polyps, adenomas, colon cancer, ulcerative colitis, and intestinal motor diseases, in the lower gastrointestinal tract. Despite the lack of systematic studies on the application of AI to the detection and treatment of CRC, the continued growth of AI applications in the medical field suggests that AI will eventually be used for the diagnosis and treatment of CRC.

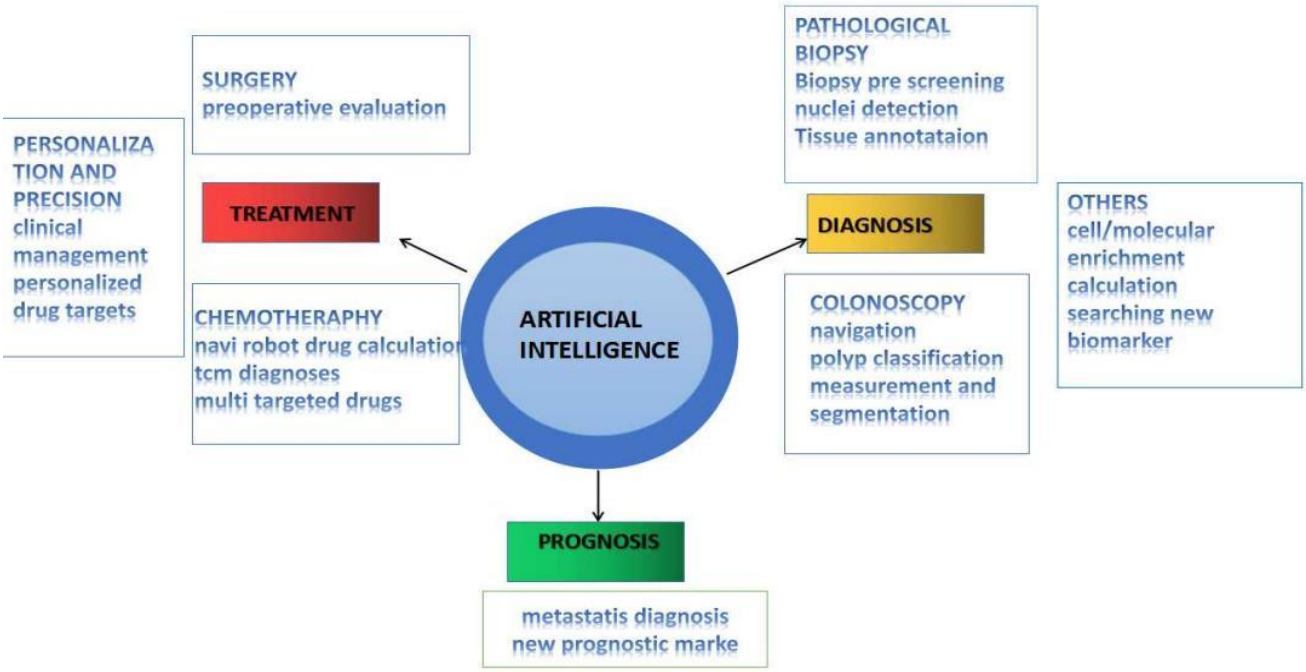


Figure10- AI's use in CRC diagnosis and treatment

4.2 Computer aided diagnosis

One promising direction for the diagnosis of polyps throughout colonoscopy is the development of an arti ficial intelligence based computer aided diagnosis system that can illustrate its choice by classifying rules designed to assist endoscopists in differentiating polyps(Chao et al., 2019). CAD is a tool that has possibility to greatly assist endoscopists in the diagnosis of colorectal polyps., detection and histological classification tasks(Komeda et al., 2017) and it is becoming a human disease diagnostic tool for the next generation because application of a computer aided diagnosis system evade the difficulties related with endoscopic resections. CAD utilizing the further in AI & particularly deep learning process provides a better alternative to human variation in production by giving predictive analytics during colonscopy(Sánchez-Montes et al., 2020). Latest versions of CAD models have a detection accuracy of 89-95% in research studies with 100-466 polyps defined per study. Some prospective studies have revealed sensitivities greater than ninety percent, with a - predictive value of 95-97 percent (Horimatsu et al., 2009). CAD of colorectal lesions using M-NBI images has been developed with the aid of new tools. This CAD program further divides Sano's colorectal M-NBI classification into three classes (group A, capillary pattern [CP] type I; group B, CP type II + CP type IIIA; group C, CP type IIIB), which classify hyperplastic polyps (HPs), adenocarcinoma (intramucosal [IM] to submucosal [SM]), and adenoma/adenocarcinoma(IM-SM

superficial) lesions and SM-deep lesions, respectively(Ikematsu et al., 2010; KATAGIRI et al., 2008; Machida et al., 2004).

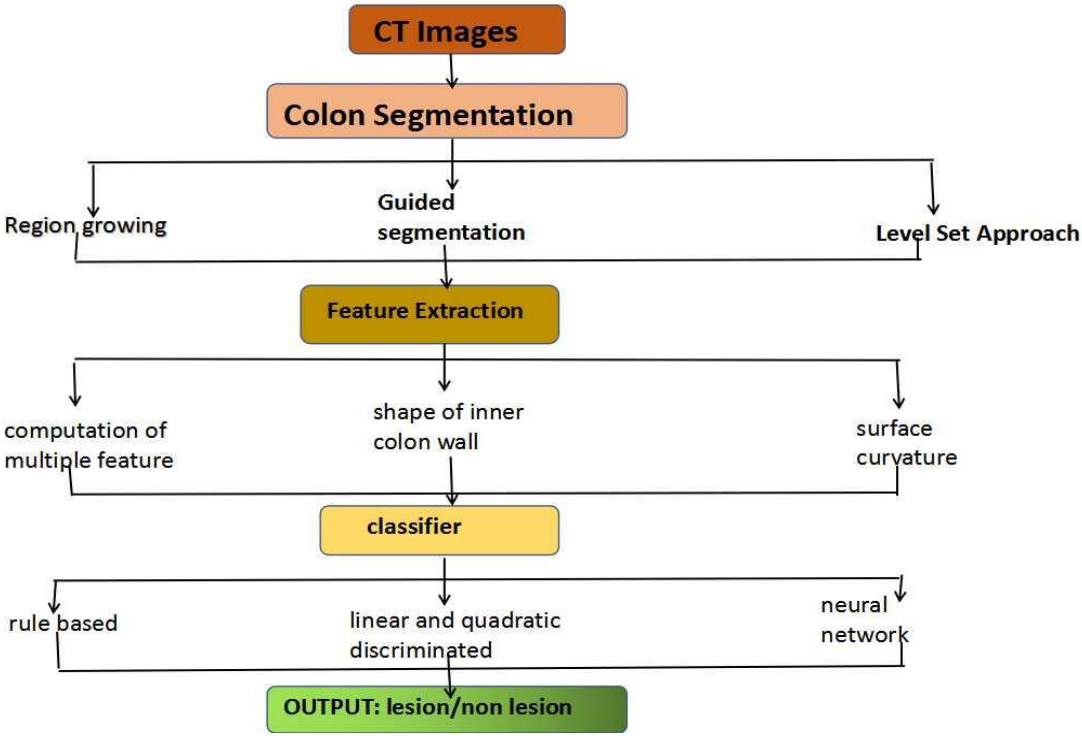


Figure11 : Layout of CAD scheme

Magnifying narrow-band imaging (NBI) allows for precise monitoring of the microvascular anatomy of lesions and further used for colorectal lesions invasion depth estimation and endoscopic differential diagnosis(Malta et al., 2018; Way et al., 2018). Machine learning (ML) and molecular docking (MD) are two e.g. of computational approaches which give novel and distinct perspectives in the battle across complicated diseases like COAD (colon adenocarcinomas). These two methods have been used widely in present to produce new findings and conclusions(Li et al., 2019; McConkey et al., 2002; Saltz et al., 2018; Salvucci et al., 2017).

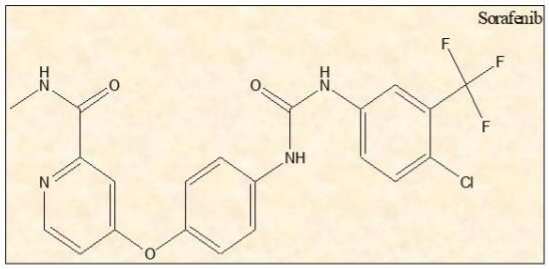
4.3 Molecular docking

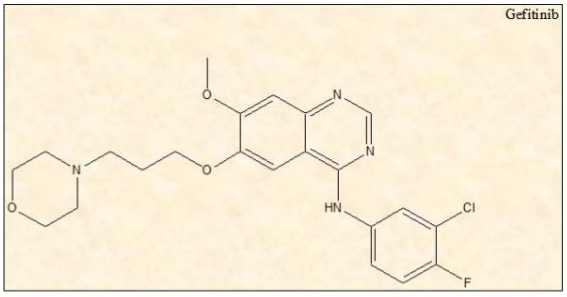
The molecular docking method is useful to analyse the interconnection b/w a tiny molecule /ligand and a protein at the atomic level, facilitating everybody to better study and grasp small molecule activity in target proteins binding sites. Binding site recognition is the technique to discover the finest-fitting ligand to the receptor and protein, and eventually a scoring feature to differentiate various binding conformation energies provided off by each ligand–protein connection are the three related components of molecular docking (Pudjiastuti et al., 2018).DOCK(Morris et al., 2018) , AutoDock(Verdonk et al., 2005), GOLD(Trott et al.,

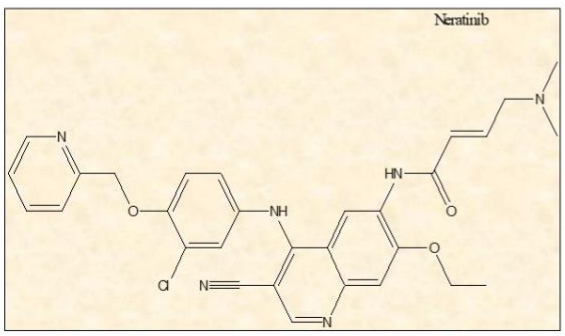
2010), AutoDock Vina(Xin et al., 2014), UCSF Dock(Misale et al., 2012), and a number of other docking software programs are available The search for phytochemical drugs that can act on EGFR as well as VEGFR, which drive the development and metastatic potential of CRC, is critical to battle cancer and aid in the development of new drug, as acquired tumour drug resistance has become a major area of concern(Arao et al., 2012; Azer et al., 2019).

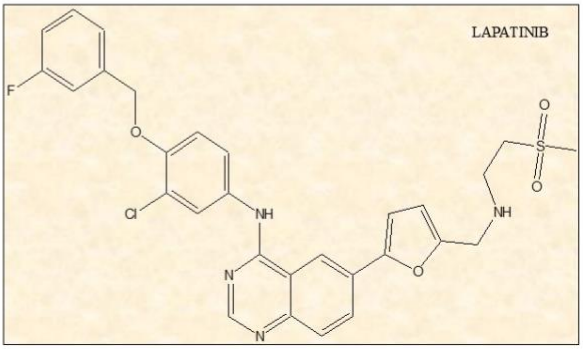
Table6: Commercially available anticancer drugs and their binding affinities with HER2,HER3, and VEGFR2

DRUG	MECHANSIM OF ACTION	VALUES		
SORAFENIB	Blocks the enzyme RAF kinase, a critical component of the RAF/MEK/ERK signaling pathway that controls cell division and proliferation; in addition, it also inhibits the VEGFR-2/PDGFR-beta signaling cascade, hence blocking tumor angiogenesis.	HER2	HER3	VEGFR2
		10.8	9.6	10.4
LAPATINIB	Reversibly blocks phosphorylation of the epidermal growth factor receptor (EGFR), ErbB2, and the Erk-1 and-2 and AKT kinases; it also inhibits cyclin D protein levels in human tumor cell lines and xenografts.	10.9	9.9	10.4
GEFTINIB	Tyrosine kinase inhibitor, e.g. EGFR, which may result in inhibition of tyrosine kinase-dependent tumor growth.	8.8	8.8	9.5
NERATINIB	Kinase inhibitor and P-glycoprotein inhibitor.	8.6	9.1	8.3









4.4 Machine learning

One of the many fields where machine learning algorithms are gaining traction is the evolution of computer aided diagnosis systems. Machine learning is the sub class of AI that refers to systems that can educate themselves using data and prior experience rather than taking direct instructions(Muhammad et al., 2019). Several experiments have been conducted to determine whether artificial intelligence can be used in computer-aided cancer predictive algorithm to decrease the chance of human fault. Decision tree are one of the most widely used traditional machine-learning algorithms in medical data analysis, they are most well-known & successful machine learning technique, with a simple architecture that produces accurate result. Support vector machines are another machine learning technique that has recently acquired importance in cancer detection applications. SVMs were found to be effective in detecting breast cancer also (with a 95% accuracy rate) and multiple myeloma, according to a report(Schmidhuber, 2015).CNN are perhaps the most oftenly used technique in CAD systems for medical image processing.Due to deep learning models perfection, it is used in the detection of colorectal cancer in colonoscopy images which is further compared in a detailed review. The accuracy of the models compared ranged from 96.4%, 87.3%, 96%,98%. These findings demonstrate the high efficacy of deep learning in CAD diagnosis(LeCun et al., 2015).

4.5 Deep learning technique

Deep learning is one of the mostly used artificial intelligence techniques and sub branch of machine learning. Deep learning, in general, is a method of educing beneficial features automatically by systematizing several linear and nonlinear processing units in a deep architecture. By reincarnating artificial neural networks, deep learning has improved the accuracy of many pattern recognition tasks, such as classifying objects, scenes, and various other entities in digital images(Gulshan et al., 2016; Litjens et al., 2016; Silver et al., 2017). Promising results in image-based diagnostics ranging from ophthalmology(Wang et al., 2016) to diagnostic pathology(Janowczyk & Madabhushi, 2016) have been reported in the biomedical field.. The use of supervised deep learning to quantify and classify digitised tissue samples has shown promising results in digital pathology, including for tasks previously thought to be too difficult to achieve with traditional image analysis methods(Esteva et al., 2019; Peña et al., 2013; Sinicrope et al., 2015). Despite significant effort in molecular profiling of colorectal cancer tumours(Ahmed et al., 2005; Bottac et al., 1997) visual microscopic analysis of tissue morphology, including pathologist typing and grading, as well as tumour stage assessment, remain core elements of colorectal cancer diagnostics. ANN has been used to explore a range of non-vision related methods for diagnosing and predicting colorectal cancer survival(Burke et al., 1997). The most commonly used and effective deep learning models in colon cancers are CNN and its variants, deep belief neural networks & autoencoders,. Traditional machine learning methods are primarily predicated on predefined engineering attributes and are usually only intended for a

specific set of difficulties. Deep learning algorithms, on the other side, don't necessitate precise characterstics definition rather, they rely on implicit feature definition.

4.5.1 Convolutional neural network

Convolutional neural networks (CNNs) seem to be multi-layer perceptron biologically influenced by Hubel's work on the cortex of a cat visuals (Hubel et al., 1962). CNNs are good at recognising visual patterns in raw image pixels. A CNN is a class of ANN that, instead of performing matrix multiplication in layers, uses a mathematical process known as convolution(Goodfellow et al., 2016). CNNs, the most commonly used deep learning model, are frequently experimented and even used machine learning algorithm in image analysis and processing (Litjens et al., 2017). The foremost explanation is that CNNs obtain, process even change input images while keeping spatial relationships. Because spatial connection can read the connection and interactions between cancerous tissue and normal tissue, they are a critical point in medical image analysis. CNNs are a deep learning architecture that has been implemented for image processing difficulties and is capable of adapting well to images. Layers in a CNN architecture are joined indirectly rather than directly, they are connected in form of blocks rather than connected directly. The complete guide between these blocks is same as of the visual cortex, eliminating the disadvantages of traditional methods.

5.CONCLUSION:

Colorectal cancer is one of the most common and lethal cancers in the world, ranked among the top three among all the cancer. The most crucial stage, as with any cancer, is early detection..Current issues in studies focus on novel computational methods and techniques to investigate high throughput multiplatform cancer knowledge, as well as image-based biomarkers for early cancer detection, were also discussed.Overall, our research found that computational approaches to CRC diagnosis accuracy yielded promising results. Many pathways are there in colorectal cancer, according to clinical and molecular evidence. Two of the somatic pathways resemble the faster procedure seen in people who have inherited mutations in the APC and MMR genes. Epidemiologic evidence suggests that a number of exogenous agents (such as tobacco smoke and meat) may greater the chance, whereas others (such as NSAIDS and vegetables) may decrease it. Colorectal cancer monitoring has been shown to decrease mortality and, in some cases, to avoid disease onset by removing precancerous polyps. Since there are a number of existing testing methods, colorectal cancer screening is available in most countries. As a result, further international awareness of targeted screening initiatives or screening guidelines may help to decrease the global load of CRC.

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