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A Review on the Ongoing Drifts of Molecular Biomarkers in VariousSpheres of Skin Cancer Prognosis

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ABSTRACT:
Skin cancer is one of the most commontypes of cancer prevalent around the globe. There are two major forms of skin cancer namely melanoma and non-melanoma (NMSC). Under the domain of non-melanoma skin cancer, there exists a wide spectrum of disorderslike squamous cell carcinoma (SCQ), basal cell carcinoma (BCC), Bowen disease (BD), Merkel cell carcinoma, etc. to name a few. The wider abundance of NMSC has in turn attracted enormous research impetus globally. The NMSC has also been reported to have various inimical traits like invasiveness, periodic recurrence, metastases, inability to recognize, etc. Accordingly, an ardent need for a clinically and economically favorable approach to prognosis was recognized to be the ardent need of the hour. The present review put insights into the major pathological aspects of NMSC along with the various molecular markers available for the same like telomerase activity (TA), telomerase length (TL), and micronuclei frequency (MNF), etc. to name a few. The assessment of these strands is cardinal for the proper management of NMSC. Thus, the present study is aimed to address such gaps and thereby would be beneficial towards assisting futuristic developments in the field of diagnosis, and prognosis of various molecular biomarkers in this domain.Matrix metalloproteinases are key molecules required for proteolytic splicing of the tissue structure, which promotestumour cell migration and participates in tissue remodelling, this contributes in upgrading the microenvironment of tumorous growth.TIMP is a kind of endogenous inhibitor which controls MMP. which has a role in activating and inactivating MMPs. Oncological study shows that this MMP supports tumour progression by destroying neighbouring tissues, performs in modulation of growth factors and membranebound receptors and proteins involved in inflammation, adhesion and chemo-attraction. Identification of such biomarkers has strengthened the base of future research in melanoma patients, which has been proven to be pivotal for defining the process for treating melanoma.The sun exposure necessary to promote skin cancer was an important unknown factor as sufficient knowledge was not reckoned. Angiogenesis, which means formation of blood vessel is regulated by Vascular endothelial growth factor (VEGF). Single-nucleotide polymorphisms (SNPs) could be identified in regulatory region of VEGF, which affecting VEGF activity. SCC could be easily recognised with VGF gene polymorphism.UVA and UVB rays are partially responsible for causing melanomas. This biochemical pathway is connected with Cutaneous Cancers Associated with Dysregulation of the mTOR deregulation.

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Development and precise delivery of chemotherapeutic drugs, targets the malfunction of tissue homeostasis and integrates possible clinical strategies.

KEYWORDS: Basal cell carcinoma; Epigenetics; MicroRNA; Squamous cell carcinoma; Telomerase.

I. INTRODUCTION:

Skin cancer has been reported to be one of the most predominant forms of cancer. Despite several public awareness programs, the prevalence of skin cancer is increasing rapidly[1]. Primarily skin cancer can be primarily categorized under two variants namely MNSC and malignant melanoma. The NMSC can be further classified into five variants namely, basal cell carcinoma (BCC), cutaneous squamous cell carcinoma (cSCC), Bowen disease (BD), and actinic keratosis (AK), and Merkel cell carcinoma (MCC) [2]. The BD has been reported to be in-situ in nature. The AK has been reported to be associated with precancerous bruises and abrasions which in turn act as the SSC precursor. The BD and AK have been reported to differ in their histopathological perspectives[3]. Although the SSCs have a notable metastatic rate, the BCCs do not show anythingsuch.Among the various types of skin cancers, BCC is predominant andprimarily arises from the stem cells located within the hair follicles[4]. BCC is a slow-growing tumourthatmight result in metastasis if left untreated. The next predominant form of skin cancer after BCC is SSC[5]. Generally, SSC occurs in areas that are exposed to intense sunlight. SSC can also generate from chronic inflammationand can be life-threatening if left untreated [6].In NMSC, BCC shows least aggressiveness and it is characterised by epidermal basal cells. Although the development of BCC by the effect of UV ray is highly controversial topic which needs more experimental data, but this play stupendous role in BCC [7]. Metastasis is a premium character which shows atypical proliferation of squamosal cell. The recurrence of tumour solely dependent on the tumour size, depth of tumour, perineural invasiveness and histological differentiation. MtDNA4977 plays a crucial role in the development of NMSC, as the basal cell carcinoma bears three times more genetic material in case of sun exposed skin. Genetic alterations result into sporadic BCC which affect the sonic HedgeHog and Ptch1 signalling pathways. More than 50% of melanoma patients possess mutation in serine and threonine kinase in BRAF. V600E point mutation is an important feature found in almost 90% cases studied on BRAF. Forkhead Box protein FOXM1 is found to be mutated in sporadic basal cell carcinoma which in turn proliferates the tumour cells. Over expression of Cyclooxygenase2 or COX2 is marked in recurrent BCC. This increases the vascular endothelial growth factor A and Mcl 1 and Bcl 2 which are potent apoptosis regulators [8]. A rare type of MCC is NMSCwhich arises from Merkel cells and banks on several factors like age, sex, and exposure to radiation to name a few. The mortality rate of MCC has been reported around 30% [7]. Over last 20 years, the BCC and SCC have increased by 35% and 133% respectively. The primary manifestation of SCC is Actinic keratosis, found to be extremely common found mostly in adult, mostly over 40 of the population.

As per updated literature reports, a wide range of factors was found to be linked with NMSC development. Among various other contributing factors for NMSC development, the impact of UV light, genetic background,and infectious agents are notable [9]. The NMSC being a multifactorial diseasehas been a challenge for medical practitioners and researchers.When the long non-coding RNA becomes abnormally expressed the metastatic growth gives rise to cancer cells.

MAJOR AIMS OF THE STUDY:

The major aim of this discussion is to focus on the multidimensional array of skin cancer prognosis and mark the crucial factors for further research work. These are:

- AK and iSCC both modify the active state of P53 gene. The genetic change produces hyperchromatic as well as pleiomorphic alteration with nuclear-cytoplasmic ratio, this results in loss of polarity and super positioning of the cell.
- To determine the progression of SCC in situ, iSCC and metastatic phase, cyto-characteristics of AK is a key factor. Development of SCC from AK can be described though various stages of keratinocyte intraepidermal neoplasia (KIN).
- The expression of cell surface HLA protein is reduced in SCC; hence HLA-I shows reduction in antigen presentation to CD8+ T lymphocytes. As a result, T cell mediated destruction of tumour cells are down regulated.
- Alteration in the APC (adenomatous polyposis coli) Gene is reported in various neoplastic individuals. APC performs a crucial role in assembling the microtubule which leads to destruction of β-catenin. This activates the transcription of Myc, Cyclin D1 and other oncogenes.
- Individuals over exposed in UV rays show allergy and inflammation as well as

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immunosuppression, cellular oxidative stress, photo-aging and their drug sensitivity is increased. The level of phosphatidyl-inositol 3-kinase(P13K) becomes upgraded when keratinocytes are over exposed in UVA and UVB radiations.

CLASSIFICATION OF SKIN STEM CELL:

Skin stem cell can be subdivided into follicular stem cell, Melanocyte stem cell, Sebaceous gland stem cell, mesenchymal stem cell, Hematopoietic stem cell and Epidermal stem cell. The Follicular stem cells give rise to melanocytes and epithelial cell lines. The melanocyte has specific bio markers such as CD200, K15,CD34,NFATC1,K19. The melanocyte stem cells show biomarkers as Dct, Sox, PAX3. Sebaceous gland stem cells widely distinguished with CD34+, K15+, Lgr6+. The Mesenchymal stem cells are exclusive with CD70, CD105. It differentiates into adipocyte showing CD73, Osteoblast showing CD105, Chondrocyte exhibiting CD90 [4]. Thehematopoietic and epidermal cells differentiate into erythroid and myeloid progenitor cells.Depending on the origin of cutaneous melanocytes, melanomas are classified as cutaneous and non-cutaneous. It is consisted of various subtypes such as acral lentiginous (occurs less than 5%), lentigo maligna melanoma (occurs 4%-10%), nodular melanoma (occurs 15%-30%) and superficial spreading melanoma (found almost 70%) [10].

The normal stem cell and cancer stem cell both shows the cell surface markers like CD29, CD44, CD133. But the cancer stem cells(CSC) are exclusive with CD133, CD44, IL6R,ALDH markers.Mutated BRAF promotes the activation of MAPK pathway. Inhibiting BRAF could lead to a new path for treating melanomas. The cytokines of immune system play a very important role in skin cancer prognosis. The IL6 acts on the non-stem cancer cells and with its positive regulation the non-stem cancer cells give rise to cancer stem cells(CSC)[2].

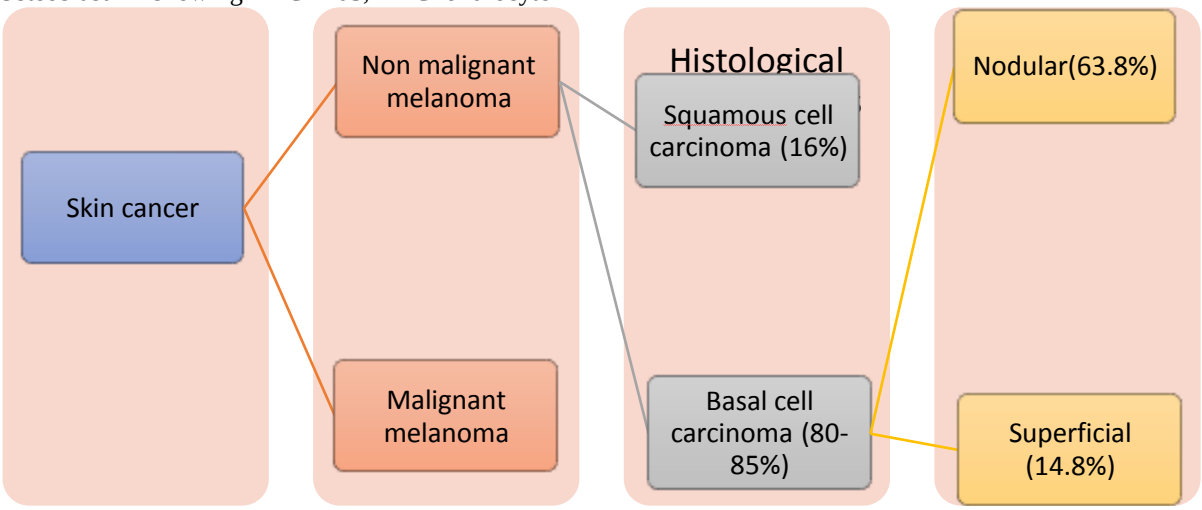

Fig.1. Differentiation of skin cancer. (Yellow colour indicates the Keratinocyte carcinoma)

CURRENT MOLECULAR BIOMARKERS:

1. Telomere Length (TL)-telomere is located at the end cap of DNA. The repetitive cell division leads to degradation of chromosomal end. As a result of telomere shortening the cell goes under senescence. The noble function of telomere is to guard the end cap of DNA in association with other specific proteins. Both the Ttl and telomerase activity is subjected to cancer cell biomarkers. Research has shown that the neoplastic cells strikingly showcase longer telomeres. The TL is determined using Q-FISH in neoplastic epidermal cells [11].
2. Telomerase Activity (TA)- the telomerase completes its function with its two sub units. The catalytic subunit is hTERT and the regulatory subunit which performs the de novo synthesis of telomeric DNA sequence is TERT. There is an array of genes which regulate the expression of TERT, these are API, NFkB, Rb/E2f, CEBP-alpha, c-Myc, Mad1, KLF4 [8]. The Wnt/B catenin pathway and estrogen receptors are also regulates the telomerase activity. The main regulatory checkpoint of TA is at its transcription. The length of telomere is larger in embryonic condition. With the development of the embryo it starts reducing and post embryonic condition it is almost diminished.

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In case ofSCC, relatively higher telomerase activity is found in compared to BCC. A close association is observed between hTERT and TA[8].

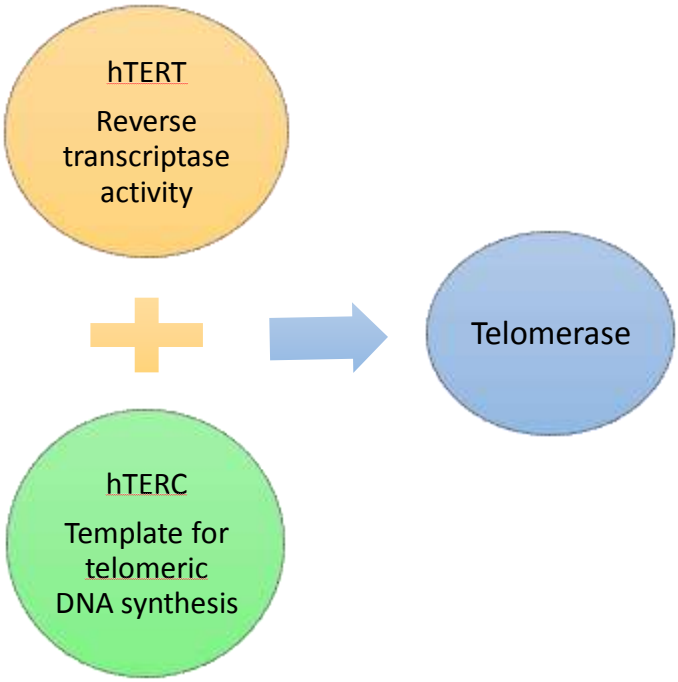

Fig.2. Structural and functional units of telomerase

3. Epigenetic Modifications- Epigenetics refers to the heritable genomic alterations which are not produced by any change in DNA sequence.Thelargecluster of CpG dinucleotide found in Dna are termed as CpG islands. Histone methylation and acetylation play crucial role in epigenetic modifications.DNA methylation generally occurs in the C5 position of cytosine ring of promoter of CpG island of a specific gene. The miRNA mediated gene regulation also widely play role in cancer stem cell [8].

a. **Modification in histone-**There are various changes occur such as methylation, acetylation, phosphorylation, sumoylation, uquitinylation. histones are mainly 5 types- H1, H2, H3, H4, H5. The H2 is subdivided into H2A and H2B. the H2A, H2b, H3, H4 altogether forms the octameric nucleosome structure around which DNA is wrapped and H1/H5 seals the structure. Acetylation in this nucleosome model creates space for the transcription factors to reach to the DNA. Methylation/ deacetylation leads to strong attachment between the two, hence there is no space left for the transcription factors to work on [5,11]. The histone is mainly methylated on lysine and arginine residue of H3 and H4 tails. The up regulated acetylation leads to reactivation of silenced tumor suppressor gene Cip1/P21 and P16. In aggressive BCC the EZH2 gene is found to be activated. The activated H3K27me3 and 5hmC are positively associated with benign phenotype of skin cancer. Basal cell carcinoma and non-malignant epidermal cellshows difference between the up regulation of NSD2, MOF, H3K27me3 and 5hmC. The cutaneous melanoma evolves from neoplastic melanoma when it is associated with H3K4 methylation.

b. **CpG island methylation (CIM)**-genomic hypomethylation results into genomic instability which promotes the activation of oncogene. As aresult of genomic instability various number of tumor suppressor gene are silenced due to hypermethylation in CpG island. The hallmark biomarkers are distributed among promoters, transcription factors and signaling pathways. The notable promoters are CDKN2A, CDH1, CDH13, FOXE1. Transcription factors such as FOXE1 and modulators of Wntsignaling pathways SFRP and FRZB, positive regulators of apoptosis such as ASC,GOS2,DAPK1, miRNA204 and DSS1 gene also play important role.

c. **MicroRNAs (miRNAs or miRs)-** MicroRNAs are single-stranded small non-coding RNAs. Variety of cancer cells actively secrete

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miRNAs into circulation. MiR-203 specifically expressed in epidermis. It is down regulated in BCC. c-JUN, a potent oncogene inhibits the expression of miR-203. In contrast miR-203 also gives negative feedback to c-JUN. synergistic oncogenic activity of sonic Hedgehog in association with EGFR suppresses the activity of miR-203. Activation of the Sonic Hedgehog and EGFR pathways, in addition to a potential crosstalk between c-JUN them may result in BCC formation. The BCC patients show low miR-34a, which performs to enlarge tumor diameter, absence of lymph node infiltration. In SCC numerous miRNAdysregulated which target key genetic modulators such as GRHL3, HOXA9, RhoBTB, AKT/mTOR pathways [12].The carcino protective miRNA regulate the genes BCAM, FZD6, DD1,ERK, MAP kinase.

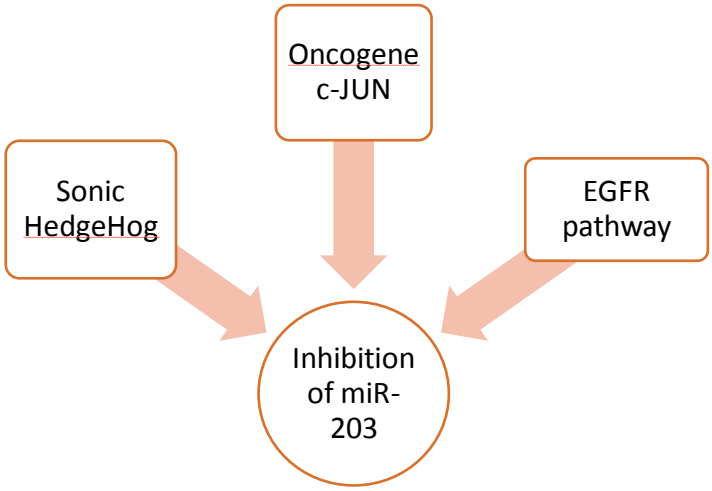

Fig.3. Interrelation between various pathways by means of skin cancer prognosis

FACTORS INDUCING SKIN CANCER:
GENETIC:

In basal cell carcinoma, tumor suppressor genes or proto oncogenes such as PTCH1 and SMO of sonic hedgehog pathway, TP53 and members of RAS family plays a crucial role. In SCC, the mutation of tyrosine kinase receptors (epidermal growth factor receptors, fibroblast growth factor receptors, certain cell regulatory genes (TP53, CDKN2A/RB1, CCDN1, MYC), RAS/MAPK and PI3K signaling pathways have a synergistic effect. The genomic loci of TP53, SoX2, NFR2 implicated in squamous cell fate determination. Notch and Fat1 have a positive role in squamous differentiation network [9,10]. Common forms of melanomas are associated with both Low Penetrance Gene (MCIR) and High Penetrance Gene (CDK4, CDKN2A, POT1, TERT, and BAP1). In almost 2% of MM patients CDKN2A is most common mutation.

According to the National Cancer Institute database, http://www.cancer.gov, the non-melanoma skin cancer can be categorized with respect to basal cell carcinoma and SCC.

Table 1. Type of SCC and responsible mutant gene.

Squamous cell carcinoma			
Responsible gene	**Mode of transmission**	**Function**	**Disease**
XPA-XPG, XPV	AR	Nucleotide excision repair Replication of damaged DNA of the leading strand	Xeroderma pigmentosum

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TGFBR1	AD	Growth factor signaling	Ferguson-Smith syndrome
COL71A	AR, AD	Collagen anchor of basement membrane to dermis	Epidermolysis bullosa (dystrophic)
BLM/RECQL2	AR	Chromosomal stability	Bloom syndrome
EVER1/EVER2	AR, AD	Signal transduction in endoplasmic reticulum	Epidermodysplasia verruciformis
TYR, OCA2, MATP/ OCA4, TYRP1	AR	Melanin synthesis	Oculocutaneous albinism
LAMA3, LAMB3, LAMC2, COL17A1	AR	Collagen anchor of basement membrane connective tissue	Epidermolysis bullosa (junctional)
RECQL4, C16orf7	AR	Telomere maintenance and trafficking	Rothmund Thompson syndrome
FANCA, FANCB, FANCC,FANCD1/BRCA2, FANCD2, FANCE, FANCF, FANCG/XRCC9, FANCI, FANCJ/ BRIP1, FANCL, FANCM, FANCN/ PALB2	AR, XLR	DNA repair	Fanconi anemia
WRN/RECQL2	AR	Chromosomal stability	Warner syndrome
DKC1, TERC, TINF2, NHP2/NOLA2, NOP10/ NOLA3, TERT, WRAP53	XLR, AR, AD	Telomere maintenance and trafficking	Dyskeratosis congenital

The genetic variations of NMSC causing an array of SCC is discussed in the above table. These skin lesion may be autosomal recessive, autosomal dominant and X-linked recessive and all three in the same time. The reason behind the phenomena is true affected gene loci of the individual. As an example, the disease Epidermolysis bullosa can produce two different forms, such as if the loci 3p21.3 is affected, the collagen of basement membrane anchors to dermis, resulting into dystrophic condition which can be autosomal recessive and dominant. In Epidermodysplasia verruciformis, loci 17q25 is affected of EVER1 gene it produces autosomal recessive character. While, EVER2 gene goes for autosomal dominant characters [11].

Table 2. Type of BCC and responsible mutant gene

Basal Cell Carcinoma			
Responsible gene	**Mode of transmission**	**Function**	**Disease**
PTCH1 PTCH2	AD	Component of HegdeHog signaling pathway	Basal cell nevus syndrome
Unknown	AD	Might be the DNA repair and cell cycle regulation	Rombo syndrome
Unknown	XLD	Unknown	Bazex-dupre, Christol

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			syndrome

In basal cell carcinoma the diseases are autosomal dominant and X-linked dominant where more researches are required to understand the biochemical regulation and functions of the responsible genes more vividly.

NON-GENETIC:

UV radiation: UV exposure from sunlight and tanning beds cumulatively causes cutaneous carcinogenesis which alters the expression of protein present in skin cells. It triggers cellular damage, as the cell mediated immune response is reduced and profound expression of reactive oxygen species.Radiation of ultraviolet ray causes the depletion of langerhans cells from epidermis.as a result, the antigen presentation in lymph node becomes altered. This causes a shift towards Th2 response. This cascade promotes the development of tumour antigen specific T regulatory cell [13]. In turn the immune surveillance is blocked which ultimately causes tumour outgrowth. UV radiation affects both indoor and outdoor workers. Outdoor workers such as agricultural workers, landscapers,postal carriers, construction worker, farmer and indoor workers like cosmeticians, metal cutting workers,welders,paint processors, laboratory technicians get affected by natural and artificial UV lights.Reactive oxygen species and nitrogen intermediates causes oxidative damages to DNA. Cutaneous nitric oxide and NO synthase are increased in cellular environment by the effect of UVA and UVB. As a result, peroxy nitrate is synthesized which acts perilously to DNA mutation.

X-ray:X-rays are ionizing radio waves used in therapeutics, excessive use of which could lead to a risk of BCC and SCCs. The radiations ionize the chemical bonds and produce free radicals, which damages lipids, nucleic acid and other cellular structures.

Arsenic: There are few such occupations which expose the workers to direct arsenic pollution which may lead to fatal skin lesion. Pesticide production and application, timber treatment and usage, mining and smelting, alloy manufacturing, battery manufacturing, glass and paint manufacture and utilization, coal fired power plants are the potential sources of insecticide, herbicides, wood preservatives, ammunition, ceramics, pigments,metal ores including copper, lead, zinc, coal combustion are hazardous to living being [9]. Metabolic pathways of inorganic arsenic consist of reduction and methylation which involves glutathione(GSH) and s-adenosylmethionine(SAM) which is an electron / methyl donor. Reductase (GST01) and methyl transferase acts as catalysingenzyme.Experiments showed that in vitro arsenic exposure increased the expression of keratin 7 and keratin 9 proteins. The topical application of 12-ortho-tetra decanoyl phorbol elevates the S100 proteins A8 and A9 which are proven inducers of carcinogenesis.

Infectious Agents: For NMCS HPV, EBV, Merkle cell polyoma virus (MCPyV) plays important role for developing neoplastic skin lesions. In immune suppressive patients β HPV is considered as a cofactor in pathogenesis of SCC. Among which the subtype β HPV species 2 is of higher risk.HPV produces E6, E7 oncoproteins which integrate into host's keratinocyte genome. The EBV is associated with chronic infections. It augments the result driven from genetic and epigenetic changes in keratinocyte genomes. Most of the MCC cases are linked with MCPyV, which is associated with carcinogenesis that does not rely on P53 pathways. MCPyV produces large T antigens (LTA) and small T antigens (STA). LTA binds tumour suppressor proteins (P53), proteins of Rb family(Rb1, RBL1, RBL2) [11,14]. Transplantation induces 30-80-fold more risk in recipients on the development of NMSC. Whereas the risk of BCC is only 10-fold, SCC shows almost 65-fold risk by the heterogeneous expression of class I HLA proteins.

Table 3. Comparative analysis of cancer-causing virus and their mode of action.

Infectious agents	Target	Mode of action
Human papilloma virus (HPV)	Keratinocyte genome	Incorporation of oncoproteins E6, E7
Epstein Barr Virus (EBV)	Keratinocyte genome	Genetic & epigenetic change
Merkel Cell Polyoma Virus (MCPyV)	P53, Rb1, RBL1, RBL2	Production of LTA & STA

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DIAGNOSIS OF SKIN CANCER AND ROLE OF MOLECULAR MARKERS:

In case of melanoma, there are few procedures involved:

1. Pre-processing or removal of hair and external structures covering the suspected lesion.
2. Segmentation of skin lesion for accuracy of diagnosis.

Evaluation of lesion is done via implementation of "ABCD" rule. The dermoscopic algorithm for inspection and identification of melanocytic lesion is – Asymmetry, Border, Colour, Diameter. In cancerous tissues S100 protein family is a potent indicator as it is over secretive in the cells [15].

Dermoscopy is a non-invasive method, where a lens is used (a lens system) and a strong lightsource, which enables to distinguish typical skin cancer skin changes.Hong and Sean-Jeannet collected experimental value on the interaction of nestin in diseased condition in melanoma patients. In sentinel lymph nodes immune-histochemistry profile emphasizes on SOX10 as biomarker which possess high specificity if conjugated with melan A and S100B like immune-histochemical stains [16].

In case of BCC, clinical onset of BCC manifestationoccurs 15-20 years after the time of UV damage. It can also occur in response to pesticide contaminated water, radiation therapy, arsenic exposure, tissue scarring, clinical history of cutaneous disease. Mutation the PTCH1, P53, CDKN2A genes are found in basal cell carcinoma.Loss of 5-Hydroxymethylcytosine is a diagnostic character of MM and differentiates the histologic and genetic aspects of melanoma subtypes which have high specificity. Resistance against the BRAF inhibitors is controlled by the involvement of hepatocyte growth factor (HGF), which in turn up regulates GAB1 and c-MET which activates the MAPK pathway [8,10].

The squamous cell carcinoma occurs with excessive sun light exposure, exposure to genotoxic substances like arsenic and cyclosporine, tobacco smoking which is also a potent environment risk factor.1.5mg Tissue from stratum corneum is collected which consists almost 23ng of rna of skin's underlying neoplasm and this may be callednon-invasive adhesive patch"skin biopsy" (2 gene expression profiling).

MSC and NMSC can be diagnosed with dermoscopy with the help of the device dermo scope. Skin biopsy may be executed in molecular and imaging technique. Depending on the degree to which suspected lesion is removed, the procedure can be divided into incisional / partial and excisional/complete [14]. In incisional process the tumour is incompletely removed and resection of the entire neoplasm is done in excisional process. Scoop biopsy is the most common excisional technique used.23-Gene Expression Profiling popularly known as Myriad Genetics is a test which differentiates benign melanocytic naive from malignant melanoma [17].

The pathology report is generated on the basis of critical details of the lesion, considering the size, maximum tumourtichness, presence and absence of ulceration,mitotic rate in the cell,evidence of malignancy along the peripheral and deep margin.Penetrance of tumours inside the dermal layerwith varying stages is determined with the help of Breslow Classification. Stage I refers to the infiltrated up to 0.75 mm, stage II refers to 0.76–1.5 mm, stage III determines 1.51–2.25 mm, stage IV shows 2.26–3.0 mm and stage V detects deeperpenetrance, which is more than 3.0 mm.

Tumours degree of advancement is determined on the extent of microsatellite metastasis into dermis and subcutis or proximal to the neoplasm. Few more important facets also considered is if the tumour could be separated from healthy tissue by at least 0.3 mm. Histological evaluation is referred as the gold standard. All the factors indicate tumour's degree of advancement [18].

Histologic interpretation of cytomorphologic and architectural characteristics, is the standard of acceptance in melanoma diagnostics.

• myPath Melanoma, 23-Gene Expression Profiling (Myriad Genetics): A test to distinguish between benign melanocytic naevi and malignant melanoma.

• Pigmented Lesion Assay, 2 Gene Expression Profiling (Derm Tech): Collection of 1.5mg of the stratum corneum tissue which contains approximately 23ng of human skin RNA from underlying melanocytic neoplasm and performing a non-invasive adhesive patch "skin biopsy".

• DecisionDx-Melanoma,31-Gene Expression Profiling (Castle Biosciences): This test from Castle Biosciences assesses the risk of metastasis in cases where melanoma has previously been diagnosed.

• FISH Testing: FISH is a molecular technique that detects complementary genomic DNA sequences on metaphase and/or interphase nuclei in tissue sections using fluorescent DNA locus-specific probes, enabling for direct viewing of specific genomic DNA segments. For melanocytic lesions, there are two types of probes: centromere probes, which identify centromeric areas on chromosomes, and locus specific probes, which hybridize onto

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target sequences spanning genes or regions of interest.

• qRT-PCR: This technique entails transcribing RNA to complementary DNA (cDNA) and then performing real-time PCR. Transcriptome data from extensive-expression array experiments can be analysed for substantial changes in RNA expression between neoplasms and used to create gene expression signatures that distinguish between benign and malignant tumours

TREATMENT:

1. According to American Academy of Dermatology excision of tumour is primary line of treatment.
2. For CMM, surgical resection is considered as gold standard.
3. In medically inoperable site, non-surgical therapy, radiation therapy and topical treatment modalities are the alternative option.
4. For the eradication of LM imiquimod 5% cream is prescribed [18].
5. Evodiamine is derived from Evodiae fructus, which is considered as a prime natural alkaloid. Treating the patients with Evodiamine promotes cell death with A375-S2 marker which is mediated through PI3K-Akt-caspase and Fas L, NF-κBsignalling path [19].

TYPES OF BIOMARKERS IN THE PROGNOSIS OF SKIN CANCER:

• 5-Hydroxymethylcytosine: 5-hmC loss has been proven to be a diagnostic feature of malignant melanoma and discriminate between a spectrum of histologic and genetically diverse melanoma subtypes and benign nevi with high sensitivity and specificity. • Prognostic Biomarkers: The Castle DecisionDx assay is a commercially available prognostic and diagnostic tool. It can identify patients with stage I and II cancer at a higher risk of metastasis and mortality. Ki-67 is a nuclear antigen expressed throughout the cell cycle's active phases and is a proliferation marker (G1, S, G2, and M). The ki-67 expression has been shown to connect directly with prognosis in thin melanomas (less than 1 mm) and may link more strongly with prognosis than mitotic count.

• Stem Cell Like Markers: A strong relationship between nestin expression and advanced disease in several melanoma specimens has been reported by Hong and Sean- Jeannet. The immunohistochemistry profile of SOX10 is a reliable marker for diagnosing metastatic melanoma in sentinel lymph nodes, with increased specificity and sensitivity when combined with additional immunohistochemical stains, including melan A or S100B.

• Inhibitors of Endogenous Markers: Tissue inhibitors of metalloproteinases (TIMPs) such as TIMP1, which are endogenous inhibitors of MMPs, are important in tumour formation. TIMPs are involved in differentiation, apoptosis, angiogenesis, extracellular matrix degradation, and proliferation of normal and malignant cell.

• Cyclooxeygenase-2: Cyclooxygenases convert arachidonic acid to prostaglandins. Cyclooxygenase-2 is activated in tumour cells. In melanoma, Becker et al. reported an association of the staining magnitude of cyclooxygenase-2 with Breslow depth. Additionally, Kużbicki et al. found that compared with benign nevi, melanoma lesions had a higher cyclooxygenase-2 staining intensity.

• Lactate Dehydrogenase: LDH is primarily secreted in response to cell death or injury, indicating increased tumour burden and disease progression. In patients with metastatic melanoma treated with ipilimumab, the baseline serum LDH level is a strong predictor of overall survival.

• Matrix Metalloproteinases: Matrix metalloproteinases are necessary for proteolytic splicing of the sectarian tissue framework, which allows tumour cell migration and promotes tissue remodelling, contributing to modifying the tumour tissue microenvironment. MMPs are regulated by a type of endogenous inhibitor known as TIMP, which has a role in activating and inactivating MMPs. MMPs have been found to promote tumour progression by degrading surrounding tissues, modulating growth factors and membrane receptors, as well as inflammatory proteins, adhesion molecules, and chemo-attractive proteins, according to oncological studies.

• Tyrosinase: It is a melanin secreting enzyme found in melanocytes and melanoma cells. RT-PCR can detect tyrosinase mRNA grades in the blood samples of patients with melanoma and late stage metastatic illness. Distribution and expression of type 3 copper protein Disease Markers 7 tyrosinase on tissue microarrays of skin samples of patients with melanoma using scanning electrochemical microscopy establishes the relevance of Tyrosinase as a molecular marker.

• Aldehyde dehydrogenase 1 (ALDH-1) is a potential therapeutic target and biomarker of stem cells in several human neoplasms, including melanoma.

• S100 Proteins: The S100 protein family is a distinct diagnostic indicator in cutaneous melanoma because of its over-secretion and over-expression in cancerous tissue.

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Identifying these protein biomarkers has laid the foundation of future research in patients of metastatic cutaneous melanoma as they can be pivotal to defining the prognosis for treatment.

THERAPY:

i. Biomarkers of MSC which can be targeted is ABCB5+. Monoclonal antibody against ABCB5+ is used, but there is a possibility of chemoresistance induced by this ABCB5.
ii. IFN-gamma-2b, cytokine IL2, tumour vaccine can be used for the target specific induction to melanoma.
iii. Melanoma cells produces T cell based immune invasion which suppresses IL2 production. this reactivates anticancer immune response [14].
iv. Ant vasculogenic mimicry therapy (VM) blocks the molecular and biochemical pathway of VM. This inhibits the tumour plasticity. This treatment remodels the tumour microenvironment by remodelling ECM.
v. DC based vaccines are used widely.
vi. Antibody therapy (Rituximab) based on cell surface markers of MSC namely CD20 is under clinical trial.
vii. Host T cell can be negatively regulated by the activity of cytotoxic T lymphocyte antigen 4(CTLA4) with its ligand B7-2 involving the upregulation of ABCB5 MSCs.
viii. Anti CTLA4 monoclonal antibody (ipilumab, tremelimumab) is used in metastatic melanoma.
ix. IL6 reduces self-renewalof MSC and induced differentiation.IL10 promotes self-renewal ability of MSC. By blocking IL10 receptor, MSC could be sensitized by only IL6, as a result MSC stops self-renewal [19].
x. TSC is activated and differentiated into chemotherapy sensitive cell type.
xi. Targeting multiple antigen against TSC/TA population either by using target specific reagent antibody or immune system activation [14].
xii. If CD133 is targeted, all TSC/TA population is destroyed, which needs additional approach.
xiii. Cryotherapy is considered as an alternative approach to Radical Excision, electrodessication, curettage, radiotherapy and the topical administration of 5-fluorouracil or imiquimod. Curettage along with diathermia are administered with electrodessication.
xiv. ALDH-1 formerly known as Aldehyde dehydrogenase 1 is apowerful therapeutic target as well as biomarker of the stem cells present in various human neoplasia, mostly melanoma [17].
xv. Nature-derived bioactive phytochemicals derived from nature could be proven to be good therapeutics in regulating PI3K or Akt or Mtor pathways to prevent melanomas.
xvi. Azole compounds such as Itraconazole is approved by FDA which belongs to the anti-fungi drug familywhich is reported to be a potential treatment for melanoma [21].

II. MAJOR FINDINGS:

Now-a-day, technology plays crucial game in medical field both in vivo and in vitro. In anti-cancer drug innovation and modification animal disease models may be coupled with high throughput drug screening. A test organized by Castle Biosciences (precisely known for Decision Dx-Melanoma,31-Gene Expression Profiling) examines the probability of metastasis in cases where patients had already suffered and cured from melanoma [16].The biomarkers represent specific molecular features of the disease of respective patient which supports the detection and diagnosis of cancer with respect to cancerous cell's biological weirdness, sensitivity to medications and drug resistance mechanisms. As melanomas of later stage shows poor prognosis, necessity of biomarker remains high who requires high end treatments.Inhibitors of metalloproteinases (TIMPs) such as TIMP1 acts as endogenous inhibitors of MMPs, are crucial in tumour formation. These are engaged in differentiation, apoptosis, angiogenesis, extracellular matrix degradation as well as proliferation of normal and malignant cell. in diagnosis of melanoma cytomorphology, its histological interpretation and architectural characters are the standard of acceptance. FISH is a popular molecular technique which detects the complementary genomic DNA sequences on metaphase and interphase nucleus which one is required from the tissue sections. It uses fluorescent DNA and locus-specific probes which enables direct observation of selected genomic DNA portions. There are two kinds of probes are used for melanocytic lesion, these are centromere probe, which identifies centromeric region on chromosome and other one is locus specific probe, which hybridizes onto target sequence,containing genes and locus of interest.The Castle DecisionDx assay tool is basically a commercially used biomarker for prognosis and diagnosis of melanoma. It can

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clearly specify stage I and II of skin cancer with higher risk of metastasis as well as mortality in patients.G1, S, G2, and M phase of the cell cycle is marked with nuclear antigen Ki-67which remains expressed throughout the cell cycle and acts as proliferation marker. The expression ofki-67 expression is directly proportional to thin melanomas (diameter is less than 1 mm) and may be connected to prognosis than mitotic count. Activated cyclooxygenase 2found in malignant cell, converts arachidonic acid to prostaglandins.Becker et al. reported the association of the staining capability of cyclooxygenase-2 with Breslow depth in melanoma cells. Kużbicki et al. discovered that melanoma lesions showhigher cyclooxygenase-2 staining compared with benign lesion. In melanin producing biochemical pathway tyrosinase plays a crucial role mostly found in melanocytes and melanoma cells. Melanoma and latestage metastasis blood samples show tyrosinase mRNA which can be detected by RT-PCR. Tyrosinase has established as a molecular marker by tissue examination focusing on the type 3 copper protein Disease Markers 7 tyrosinase [20].Keratinocyte proliferation and differentiation solely dependent on the keratinocytes-Specific protein regulatory factor 6 and alpha-2 macroglobulin-like protein2. IL-1 has sheer effect on the synthesis of angiogenesis factors and anti-apoptotic proteins. Hence, it is been postulated that IL-1 performs important character in melanomas. Naturally occurring phytochemicals and synthetic biomolecules have extensively examined for their capability to repair PI3K-Akt-mTOR pathway associated cutaneous lesions.trans-8-methyl-N-vanillyl-6-nonenamide formerly known as Capsaicin is activated compound found in pepper which restricts the metastasis and angiogenesis of B16-F10 carcinogenic cells in vitro. mTORC1 inhibitor Rapamycin specifically inhibits cell proliferation documented in various melanoma cells. Acacetin is a naturally occurred flavonoidchemically known as 5,7-dihydroxy-40 -methoxy flavone collected from Robininpseudo acacia, popularly known as black locust, is well documented antioxidant which hasanti-inflammatoryand anticancer properties.

TYPE OF ENHANCEMENTS TILL DATE:

Genes present on melanoma cells are target molecules for treatment. To treat advanced melanomas these days, BRAF gene specific drugs are administered. As HIV infection weakens immune system, intravenous drugs are administered now a day to reduce skin cancer as well as various cancers formed in the body. Genetic testing needs a whole bunch of knowledge followed by a genetic counselling.Health care professionals depict about the tests and tell the patients about the imperfections and dissimilarity between healthy cell and metastatic cells. The test does not provide clear answer. qRT-PCR is one of the most popular technique which entails transcribing RNA to complementary DNA (cDNA) followed by real-time PCR. Transcriptome data are derived from extensive-expression array of experiments which could be analysed for substantial changes in RNA structure between malignant and other skin lesions.mTOR pathway activation is recommended to make association with melanoma pathogenicity. Activated mTOR pathway inhibits autophagic cell death and the normal cell cycle starts malfunctioning.

PREVIOUS AND MODERN TECHNOLOGY OF SKIN CANCER AND FUTURE TRENDS:

i. Keeping the Hedgehog Signalling Pathway in focus, Vismodegib is the first orally selective inhibitor used for treatment. It binds selectively to the transmembrane smoothened protein which is encoded by the gene SMO. It inhibits the hedgehog signalling pathway, which in turn inhibits the tumorous growth.
ii. Pivotal ERIVANCE BCC study andSTEVIE, which is the study of Vismodegib drug in people suffering from metastatic BCC is proceeded for long period of time [14,18].
iii. Mutation in BRAF must be considered in all patients with metastatic lesion. Suggested procedures may be polymerase chain reaction (PCR) or immune histochemistry (IHC).
iv. The drug Dabrafenib enhanced the progress of free survival and median survival in stage IV MM individuals, in comparison with those individuals treated with dacarbazine.
v. An important portion of the MAPK pathway is the Mitogen-activated protein kinase (MEK) is a serine/tyrosine/threonine kinase, which is an irreplaceable way to provide therapy in melanoma patients.
vi. The combined treatment with BRAF and MEK inhibition ameliorates the apoptosis and delay the slowdown of resistance compared to BRAF inhibitors.
vii. Specific acral and mucosal subtypes of MM exhibits type III transmembrane receptorof tyrosine kinase (KIT) which activates the mutations while, Imatinib and Nilotinib treatments have shown efficacy.

viii. Interleukin-2, is one type of cytokines weight almost 15.5kDa makes bond with receptor consisted of IL-2Rα, IL-2Rβ, and IL-2Rγ. Thus, immunotherapy comes to play.
ix. For MM, treatment with IFN-α is widely used and one of the most efficient therapy. If any melanoma cells remain in the body even after surgery, this treatment evade out all those mutated cells.
x. Ipilimumab resembles to human IgGI monoclonal antibody ensures overall survival rate in melanoma. Lymphocyte associated antigen-4 (CTLA-4) becomes blocked by activated T cell in this therapy.
xi. Metastasis of distant melanoma is treated withpembrolizumab and nivolumab both of which are antibodies.
xii. T cell and NK cellsspecific for allogenic and autologoustumour are administered to individuals for achieving regression of the tumours.
xiii. Trametinib is the inhibitor of MEK1/2 pathway are well practiced medication for melanoma patients.
xiv. Various nanoparticles such as Liposomes, dendrimers, polymersomes, carbon-based nanoparticles, inorganic nanoparticles, andsome protein-based nanoparticles are considered to treat skin cancer.
xv. Magnetic nanoparticles (MNPs), size varies between 10–100 nm, gives response in magnetic field. Hence used as a medication for multimodal drug administration considering their super paramagnetic powers.
xvi. Nanotechnology opens a new horizon where treatment efficacy is high, possible drug toxicity is low, target specificity is absolute with good compliance with patients [18].
xvii. Doxil (Janssen Biotech, Horsham, PA, USA), which is doxorubicin containing liposome injection and Nab-paclitaxel (Abraxane), which consisted of paclitaxel bound albumin nanoparticles ($2r \approx 130$ nm) are approved nanotechnology-based medications used widely [22].
xviii. Theragnostic combines all the required "components" to fulfil all the requirements of the novel treatment, thus introduces a new horizon.

III. DISCUSSION:

The processes in which endothelial cells, the inner lining of blood vessel migrate and forms new blood vessel are called angiogenesis. This procedure is regulated by various protein and chemical signals of the body. Angiogenic switch refers to the predominance of proangiogenic factors. The histological specimen of tumour and tumour stroma interface higher micro vessel densities (MVD) measured [15]. VEGF is the main angiogenic factor which is higher in Basal Cell Carcinoma, compared to normal skin and SCC. VEGF is directly correlated to the MVD. Role of Biomarkers such as COX2, matrix metallopeptidase-9 (MMP9), Maspin in angiogenesis is identified by proteomic study. Tissue inhibitors of metalloproteinases (TIMP) inhibit the MMP dependant angiogenesis whereas regulators of apoptosis Mcl1, Bcl2 and CD31 show positive regulations. BCC is epidermal derived cancer which possesses the ability to metastasize but the spread is rare (0.0028 to 0.55%). Some retrospective study shows that short fine telangiectasias (SFT) (dilated blood vessel) is supposed to be a dermoscopic hallmark of BCC. (Lupu et al.,2019) the most common form of skin cancer is NMSC, though it generally does not affect survival, hence excluded from National Cancer Registries. Deregulation in Hedgehog signalling gives rise to BCC and inappropriate Wnt signalling found in different epidermal tumours. Activated mutations in beta catenin result into pilomatrixoma and trichofolliculoma. β-catenin is one of the prime oncogenes showing skin tumors after mutations. KRAS, P53, HRAS mostly responsible for papilloma and SCC [14]. The molecules and extra cellular fluid released by melanoma cells enters the blood stream and can be considered as serum biomarkers. This is consisted of enzymes, various antigens, free nucleic acids and metabolites. These play the role of specific markers [25]pH Controlled Drug Release: Mesoporous silica nanoparticles (MSNP) is a pharmacological biomolecule which releases the incorporated drug before reaching the target cell as it is regulated by ph. Hence the potentially perilous drugs cause damage in undesired cells [16]. Drug release is also regulated by temperature such as pores' plug like polymers are sensitive to temperature. Poly (N-isopropylacrylamide) (PNIPAM) is widely used drug of choice. The redox potential naturally arises when glutathione (GSH) increases up to100-1000-fold in tumour cell in comparison with its extra cellular matrix. MSNP is optically responsive molecule whose response relies on chromophore binding with MSNP. LDH is found during cell injury or death. In MM patients, serum LDH is potent indicator of survival of the cell when treated with ipilimumab. Over expressed Rictor is prime regulator of Akt

phosphorylation. In MM Rictor inhibits melanoma in liver metastasis.

IV. CONCLUSION:

Different pattern of UV exposure causes melanoma in different parts of the body, such as melanoma found on chest, back and leg could be linked with sunburn specifically in childhood. Evidential study shows that these melanomas are different from melanomas found on face, arms and neck. Melanomas may also occur on the feet, palms, beneath the nails known as acral lentiginous melanomas, mucosal melanoma found on mouth and vagina where almost no sun exposure is reached.Integrin plays prime role in angiogenesis, which is a sound character of vasculature of the tumour. The endothelium targeting could be potential treatment for recovery. Peptide covered quantum dots are programmed to target specific blood and lymph vessels. Liposomes covered with NGR are used to target tumour vessels. Procedure of therapeutic drug delivery include endothelial cell adhesion molecules (CAMs) (e.g., ICAM-1 and PECAM-1). In vivo Anti-CAM nanoparticles deliver drug molecules to the endothelium of lungs and heart. Evidences report that irregular expression of miRNAs (microRNAs) in melanoma genesis adds Uveal melanoma (UM) also.

If melanoma becomes racial, that refers to the fact that if someone from the family had suffered from melanoma, these dysplastic nevi is referred to as familial atypical multiple mole and melanoma syndrome (FAMMM). At around 10% of all individuals suffering from melanoma had a family history of this [25].

Study shows that women suffer less than men from melanoma, though it varies with age in the United States. Before age 50, the risk is higher for women below age 50 have higher risks, in contrary men above age 50 suffers more than women [26].

Melanomas possess mutations in tumour suppressing genes such as CDKN2A (formerly known as p16) or CDK4 which prevent the genes from regulating cell proliferation. This leads to cancer. Individuals suffering from xeroderma pigmentosum (XP), inherit a mutation in one of the XP (ERCC) genes, which generally help to repair damaged DNA. [27] Lower side effects and decreased dosages of drugs designed by functionalized nanomaterials due to EPR (Enhanced Permeability and Retention) promotes functional nanomaterials which works on lower dose and side effects. In tumours condition, pH., redox potential, glucose level, serum antigens and other parameters change, in turn the action of administered drug also varies. MRI with T1-T2 sensitive molecules, fluorescein biomarkers and radionuclides are used widely. Akt activation is associated with the study of transition from RGP to VGP.

LIST OF ABBREVIATIONS:

AR = Autosomal Recessive
AD = Autosomal Dominant
XLR = X- linked recessive
XLD = X-linked dominant
MSC = Melanoma Skin Cancer
NMSC = Non-Melanoma Skin Cancer
BCC = Basal Cell Carcinoma
SCC = Squamous Cell Carcinoma
BRAF= B-Raf protein
RGP= Radial Growth Phase
VGP= Vertical Growth Phase
ALDH= Aldehyde Dehydrogenase
MAPK= Mitogen Activated Protein Kinase
TERT=Telomerase Reverse Transcriptase

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