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MODERN METHODS OF MALIGNANT SKIN MELANOMA EARLY DETECTION: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Skin melanoma is the most dangerous malignant neoplasm of the skin; it ranks ninth in the structure of oncological diseases worldwide. Despite the simplicity of preventive measures and the fact that melanoma is one of the most visually detectable tumors, its incidence continues to rise globally each year. As a result, enhancing early detection and prevention strategies remains a critical public health priority. Dermatoscopy remains the gold standard for early diagnosis, serving as the foundation for all modern diagnostic equipment. Additionally, specialized genetic testing methods are available to identify familial melanoma cases in high-incidence regions.*

The study aimed to *describe the capacity of modern early skin melanoma detection methods.*

Methods: *We used specialized scientific search engines such as Scopus and PubMed to examine current methods for early melanoma skin cancer detection described in publications from 2014 to 2024.*

Results: *Dermatoscopy and confocal microscopy remain the first choices for specialized physicians due to their simplicity and accessibility. Although Nevisense electrical impedance spectroscopy has a high diagnostic value, it is inaccessible to patients and physicians. AI-based mobile dermatoscopic applications are promising because they are accessible to both parties. CDKN2A genetic testing is used in regions with a high population incidence of melanoma to detect familial malignant melanoma syndrome.*

Conclusion: *Further technological progress shall promote modern methods of diagnosing skin melanoma based on efficiency, cost-effectiveness, simplicity, and accessibility.*

Keywords: *malignant skin melanoma, early detection, noninvasive methods, familial melanoma.*

Introduction: Malignant skin melanoma (MSM) is a serious type of skin cancer that develops from melanocyte cells. Although squamous cell carcinoma is less common than basal cell carcinoma and squamous cell carcinoma, which originate from epithelial tissue, it is considered dangerous due to its ability to rapidly metastasize to other organs [1]. Melanocytes are skin cells located in the upper layer of the skin. They produce the pigment melanin, which gives the skin its color. There are two types of melanin: eumelanin and pheomelanin. When the skin is exposed to ultraviolet radiation from the sun or artificial tanning, it causes damage to the skin. As a result, melanocytes produce more melanin, which protects the eumelanin pigment from the skin, causing it to darken or tan. Modern oncology views MSM proliferation as a complex multifactorial process with a combination of genetic, epigenetic, and environmental factors that contribute to its occurrence and can be prevented [2]. MSM occurs when DNA damage by UV radiation caused by sunburn or oxidation induces mutations in melanocytes, which triggers a complex mechanism of uncontrolled cell growth. International Agency for Research on Cancer has classified solar ultraviolet radiation and tanning devices that emit artificial ultraviolet radiation as carcinogens, placing them in the highest risk category for colon cancer, alongside other carcinogens such as radon, tobacco, and asbestos. Solarium-induced melanoma affects more people than lung cancer caused by smoking [3]. According to the International Agency for Research on Cancer (Lyon, France), 325,000 cases of melanoma (174,000 cases in men, 151,000 cases in women) were reported worldwide in 2020, and 57,000 people (32,000 men and 25,000 women) died from it [4]. One important factor in the incidence of MSM is geographical location. The incidence of MSM is highest in equatorial regions and decreases as one moves north or south of the equator, which is related to the number of hours of sunlight in these regions compared to regions of greater or lesser longitude [5]. The incidence of colorectal cancer has increased worldwide, not only in the last decade but also in the past, and this increase is faster than other cancers [6]. The most alarming element of these statistics is the relatively young age of patients suffering from MSM. Unlike colorectal (68 years), lung (70 years), and prostate (71 years) cancers, the median age of diagnostics in patients with MSM is only 57 years.

The study aimed to describe the capacity of modern early skin melanoma detection methods.

Materials and methods: Data were collected from peer-reviewed sources indexed in the scientific search systems Scopus and PubMed between 2014 and 2024. A total of 48 sources were retrieved based on the keywords of the study. We also analyzed open-access articles from the European Consensus Interdisciplinary Guidelines for Melanoma Research. Of these, 15 sources were included in the analysis, providing an overview of current STI prevention methods.

Results:

Dermatoscopy and confocal microscopy. Dermatoscopy is the most common, simple, and accessible method of early diagnostics. Dermatoscopy has been shown to have a diagnostic accuracy of up to 89% compared with clinical diagnostics of skin lesions [7]. Dermatoscopy should be used for all malignant skin neoplasms, not just for clinical suspicion. This is because dermatoscopy allows the detection of morphologic asymmetry of MSM before it is clinically recognized. Dermatoscopic photodocumentation of the lesion before surgical removal is primarily recommended [8]. Dermatoscopic features of MSM are distinguished using the CASH algorithm (C-color, A-architecture, S-symmetry vs. asymmetry, H-homogeneity vs. heterogeneity), an improved version of the ABCD algorithm. These include color polychromy, irregular arrangement of structures in the dermatoscopic image, symmetry and asymmetry of patterns, and the presence of the following dermatoscopic appendages: atypical pigmented mesh, irregular brown-black dots/balls, irregular stripes and lines, white shiny stripes, "blue-white veil" feature, and polymorphic veins. Figure 1 shows the dermatoscopic image of MSM according to the clinical presentation: A - MSM on the face resembling a brown flat pigmented lesion, and dermatoscopy shows a brown pseudo grid with irregular pigmentation of follicular openings; B - Dermatoscopic image of superficially distributed MSM with brown asymmetry on the body skin shows color asymmetry, atypical globules, and pigmented mesh; C - Nodular melanoma of the body skin with a bluish hue, whose dermatoscopic image shows bluish pink color and asymmetry of structures, globules and polymorphic vessels, and white streaks. Confocal microscopy provides images of the epidermis and superficial layer of the dermis. Like dermatoscopy, it allows the evaluation of pathologic changes in skin tissue by obtaining images in the horizontal plane. In confocal microscopy, the contrast image is obtained due to differences in the refractive index of the laser beam of organelles and other cellular microstructures, which appear lighter against the background of underlying structures. Confocal microscopy is a promising practical tool for diagnosing and monitoring pigmented and non-pigmented skin neoplasms. It shows horizontal skin layers with a maximum depth of 350 μm. When examining the skin, the resolution provided by confocal microscopy is very important compared to histologic examination since lateral resolution is less than 1 μm, and vertical resolution is 3 to 5 μm.

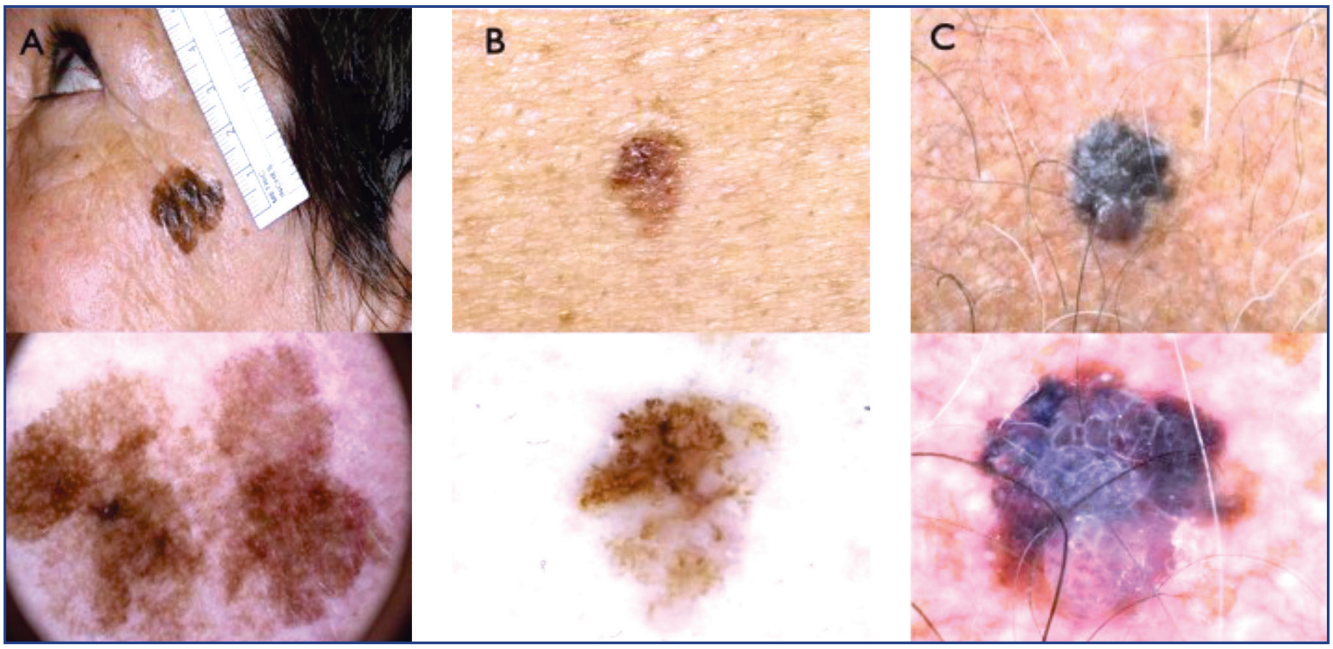

Figure 1 - Clinical and dermatoscopic picture of malignant skin melanoma

Electrical Impedance Spectroscopy. This method analyzes the electrical resistance or conductivity of materials and systems at various frequencies. The Nevisense system, which analyzes with this method, determines the degree of conductivity of skin neoplasms by passing electrical currents of different frequencies through a device similar to an ultrasound probe. Since MSM cells conduct electric current more actively and faster than healthy skin cells, this effect can be registered using spectroscopy based on electrical resistance measurements [9, 10]. Thanks to pre-established control measurements, the system allows for comparing CT scan results with measurements from the lesion area on the skin of the intended patient. In an international multicenter prospective study conducted at 5 U.S. and 17 European research centers, 256 of 265 cases of histologically confirmed squamous cell cancer were preliminarily identified by the Nevisense system using electrical impedance spectroscopy with an accuracy of 96.6% and an accuracy of 100% for non-melanoma skin cancer. Thus, the Nevisense system can be a noninvasive method for screening colorectal cancer in high-incidence countries [11, 12].

Artificial intelligence (AI) technology based on dermatoscopic applications for mobile phones. AI-based mobile applications are a simple, practical, and accurate diag-

nostics method for suspected skin cancer and squamous cell carcinoma in patients visiting oncological dermatologists. However, its use requires careful refinement of the decision-making mechanisms within the program [13]. Most retrospective studies in oncodermatology show a clear advantage of AI over humans [14]. The International Skin Imaging Collaboration 2018 Challenge study compared 10,015 computer algorithms across 7 diagnoses (MSM, nevus, dermatofibroma, pigmented basal cell carcinoma, non-pigmented basal cell carcinoma, keratosis, and benign vascular tumors). The ISIC 2018 AI algorithms were more accurate than the diagnoses of young specialists. However, the study, like almost all studies of this type, was not conducted in realistic everyday clinical settings; Instead, physicians were forced to evaluate images on a computer screen without contextual information. Thus, it remains unclear whether the benefits of IA obtained in this study will be implemented in clinical practice. The results of the ACTRN12620000695909 multicenter prospective diagnostic clinical trial conducted in Australia and New Zealand, which allowed real-time validation of the ISIC 2018 study, are described as a "new wave" of artificial intelligence in oncodermatology when compared to the ISIC 2018 AI, the AI diagnoses in category 7 in the study were equivalent to those of the leading specialists. The absolute difference in accuracy compared to the decisions of the leading specialists was 1.2%, and in contrast, it exceeded those of the young specialists by 21.5%. The balanced multi-class accuracy (average completeness score) of the above 7 diagnoses was 65.9% for category 7, 52.2% for ISIC 2018, 73.8% for leading specialists, and 35.5% for young specialists [15].

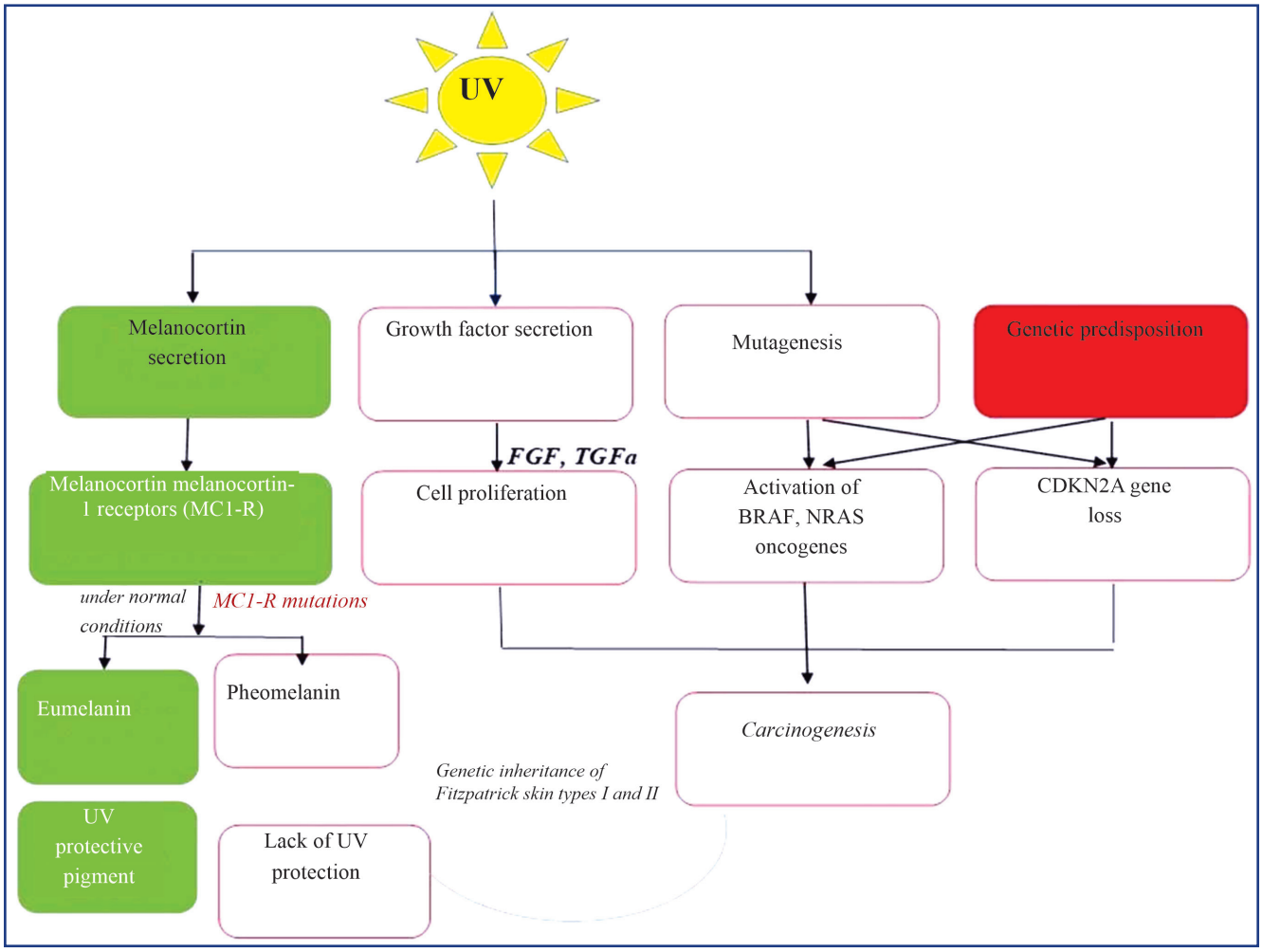

Figure 2 – Involvement of the CDKN2A gene in the pathogenesis of malignant skin melanoma

Genetic testing for the CDKN2A gene. The *CDKN2A gene*, a cyclin-dependent kinase 2a inhibitor, is located on chromosome 9. It encodes several proteins, the most studied of which are p16ink4a and p14arf, which slow cell division and act as a TSC suppressor. Normally, the CDKN2A gene is involved in the prevention of MSM, but when mutated, it increases the risk of developing MSM. Mutations in *CDKN2A*, along with multiple dysplastic nevus syndrome, cause FAMMM syndrome, i.e., familial atypical multiple myeloma inherited in first-degree relatives in the autosomal dominant type [16, 17]. Environmental factors (ultraviolet light) and genetic heredity (CDKN2A, CDK4, MC1R, BRAF, p16/ARF genes) lead to the accumulation of genetic mutations in melanocytes. As a result, oncogenes are activated, tumor suppressor genes are suppressed, and DNA repair processes are impaired [18]. This, in turn, leads to proliferation, pathologic angiogenesis, penetration of MSM into tissues, and evasion of immune re-

sponse (Figure 2). Genetic testing for MSM susceptibility genes is recommended in families with MSM after a suitable candidate has been selected and appropriate counseling has been provided to the patient. Currently, access to genetic testing depends on the geographic distribution of the disease, with 5-12% of cases being "familial" [19], and the proposed criteria for genetic evaluation are used in countries with very high incidence, such as Australia. Genetic testing of the CDKN2A gene has been available for over 20 years. However, the use of multigene panels to test for hereditary MSM is increasingly being implemented in clinical practice, increasing the ability to identify pathogenetic variants [20]. Multigene testing is particularly important if there is a family history of other cancers, as some genes predisposing to MSM may be associated with other hereditary cancers (e.g., pancreatic cancer). This facilitates a personalized approach to testing [21].

Discussion: Early detection of MSM is a challenging task that requires a multidisciplinary approach. The dermatoscopy and confocal microscopy methods presented in this article are more widely used, easier to apply, and relatively affordable than the electro-impedance spectroscopy method. Although the Nevisense electroimpedance spectroscopy method has demonstrated its superiority in detecting various types of skin neoplasms, it is not available to Onco-dermatologists and patients. The ACTRN126200000000695909 study on AI-based mobile dermatoscopic applications is the first prospective study to validate the potential of artificial intelligence-based MSM diagnostics using dermatoscopic imaging in a clinical setting for all clinically relevant classes of pigmented lesions. The importance of the study is underscored by the fact that the results were obtained using simple cell phone technology with no available hardware, unlike previous, more expensive, stand-alone devices. It is important to inform people with mutations in the "familial" MSM and CDKN2a genes about preventive measures. They should be instructed in photoprotection techniques and monthly self-examination, and for high-risk individuals, the frequency of examinations by an Oncologist or Dermatologist should be increased to once every 3-12 months.

Conclusion: Effective methods and technologies for early detection of MSM are now becoming available. However, one of the main challenges is implementing these methods in clinical practice for rational use in relation to the patient. The requirements for diagnostic methods include high diagnostic accuracy of methods, ease of use, digital registration of results and binary responses of diagnostic systems, and economic accessibility. This considers the need for training of health care providers, minimal time commitment for the patient and physician, and convenience for the patient. Unfortunately, a modern noninvasive diagnostic method that meets all these requirements has not yet been found. This situation means that the physician chooses an available method rather than an effective one for the patient. Thus, the human factor can be considered one of the obstacles to early detection of MSM.

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АНДАТПА

ҚАТЕРЛІ ТЕРІ МЕЛАНОМАСЫН ЕРТЕ САТЫДА АНЫҚТАУДЫҢ ЗАМАНАУИ ӘДІСТЕРІ: ӘДЕБИ ШОЛУ

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Өзектілігі: *Қатерлі тері меланомасы терінің қатерлі түзілістерінің ішіндегі ең қауіптісі болып табылады және дүние жүзі бойынша онкологиялық аурулар құрылымында тоғызыншы орында. Алдын алу шараларының қарапайымдылығы мен онкологиядағы визуалды түрде қолжетімді локализацияға жататынына қарамастан, терінің қатерлі меланомасымен сырқаттанушылық дүние жүзінде жыл сайын өсу үстінде. Сондықтан да, аурудың ерте сатыда анықтау мен алдын алу әдістерін жетілдіру бүгінгі таңда қоғамдық денсаулық сақтау саласындағы маңызды міндет болып табылады. Ерте сатыда анықтау әдістерінің арасында «алтын стандарт» ретінде дерматоскопия болып қала бермек және заманауи жабдықтардың барлығы да осы әдіске негізделген. Сонымен қатар, сырқаттанушылық жоғары аймақтарда «отбасылық меланоманы» анықтайтын арнайы генетикалық тестілеу әдістері де қарастырылған.*

Зерттеудің мақсаты *– тері меланомасын ерте сатыда анықтаудың заманауи әдістерінің мүмкіндіктерін сипаттау.*

Әдістері: *Scopus, PubMed арнайы ғылыми іздеу жүйелері арқылы 2014-2024 жылдар аралығындағы дереккөздерден тері меланомасын ерте сатыда анықтаудың заманауи әдістері зерттелді.*

Нәтижелері: *Мақалада сипатталған дерматоскопия мен конфокальды микроскопия әдістері қарапайымдылығы мен қолжетімділігінің арқасында, бейінді дәрігерлердің бірінші кезектегі таңдау әдісі болып қалып отыр. Невисенс жүйесі арқылы жүргізілетін электроимпедансты спектроскопия әдісінің диагностикалық құндылығы жоғары болғанымен, науқас пен дәрігерге қолжетімсіз. Ұялы телефондағы дерматоскопиялық қосымшаларға негізделген жасанды интеллект технологиясының болашағы зор, себебі екі жаққа да қолжетімді ұялы телефон негізінде жасалған. Популяциядағы сырқаттанушылық көрсеткіштері жоғары дүние жүзінің аймақтарында отбасылық тұқым қуалайтын қатерлі тері меланомасын анықтауға CDKN2A геніне генетикалық тестілеу жүргізіледі.*

Қорытынды: *Технологиялық прогрестің жалғасуымен тері меланомасын диагностикалауда заманауи әдістердің қолданылуы тиімділік, үнемділік, қарапайымдылық, қолжетімділік сияқты принциптерге негізделуі керек.*

Түйінді сөздер: *қатерлі тері меланомасы, ерте сатыда анықтау, инвазивті емес әдістер, отбасылық меланома.*

АННОТАЦИЯ

СОВРЕМЕННЫЕ МЕТОДЫ ВЫЯВЛЕНИЯ ЗЛОКАЧЕСТВЕННОЙ МЕЛАНОМЫ КОЖИ НА РАННЕЙ СТАДИИ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Меланома кожи является самым опасным злокачественным новообразованием кожи и занимает девятое место в структуре онкологических заболеваний во всем мире. Несмотря на простоту профилактических мер и тот факт, что меланома кожи относится к опухолям визуально доступной локализации, заболеваемость злокачественной меланомой кожи ежегодно растет во всем мире. Поэтому совершенствование методов выявления и профилактики на ранней стадии является сегодня важнейшей задачей общественного здравоохранения. Среди методов обнаружения на*

ранних стадиях дерматоскопия остается «золотым стандартом», и все современное оборудование основано на этом методе. Кроме того, в регионах с высокой заболеваемостью также предусмотрены специальные методы генетического тестирования, которые позволяют выявить «семейную меланому».

***Цель исследования** – описание возможностей современных методов выявления меланомы кожи на ранней стадии.*

***Методы:** С помощью специальных научных поисковых систем Scopus, PubMed изучены современные методы раннего выявления меланомы кожи по источникам за период 2014-2024 гг.*

***Результаты:** Методы дерматоскопии и конфокальной микроскопии, описанные в статье, благодаря своей простоте и доступности остаются методом приоритетного выбора профильных врачей. Хотя метод электроимпедансной спектроскопии, проводимый через систему Невисенс, имеет высокую диагностическую ценность, он недоступен для пациента и врача. Технология искусственного интеллекта, основанная на дерматоскопических приложениях в мобильных телефонах, является многообещающей, поскольку она основана на мобильном телефоне, доступном для обеих сторон. В регионах с высокими показателями заболеваемости населения меланомой кожи проводится генетическое тестирование гена CDKN2A на выявление семейной наследственной злокачественной меланомы кожи.*

***Заключение:** По мере продолжения технологического прогресса применение современных методов в диагностике меланомы кожи должно основываться на таких принципах, как эффективность, экономичность, простота, доступность.*

***Ключевые слова:** злокачественная меланома кожи, выявление на ранней стадии, неинвазивные методы, семейная меланома.*

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