Xplore Health

DISCOVER THE LATEST ON HEALTH RESEARCH

Educators' guide "Skin cancer exposed"

(Background information)

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1. Introduction

This guide will provide you with background information on the Xplore Health module “Skin cancer exposed” to enable you to prepare a lesson using the multimedia tools on the website. The latest research into melanoma, the most severe form of skin cancer, and ethical, legal and social aspects surrounding this disease are discussed.

2. State of the art

2.1. Introduction

The skin is the largest organ of the body and protects against heat, light, infection, and injury. It is made up of two main layers: the epidermis (the top layer) and dermis (the inner layer). Melanocytes are cells found in the epidermis and they contain melanin, which gives the skin its colour. Melanoma is a cancer of the skin, that originates from melanocytes. It usually occurs in adults and only occasionally occurs in children and adolescents, and is a very serious form of skin cancer.

Melanoma can occur in sites other than the skin and this accounts for 5% of melanoma cases including melanoma of the eyes or mucous membranes e.g. mouth. The cause, outcome and treatment options of these rare forms of melanoma differ from that of skin (cutaneous) melanoma.

It usually appears on the body as a new mole. Men most often get melanoma on the trunk or on the head or neck; women most often get melanoma on the arms and legs. As with other cancers, melanoma is best treated when it is found early. It can spread (metastasize) quickly to other parts of the body through the blood or through the lymphatic system (a collection of vessels which help the body to fight infection).

2.2. Epidemiology of cutaneous melanoma

The number of cases of melanoma is rising faster than that for any other major cancer. More than 10,400 cases of melanoma are identified every year in the UK with over 2,000 deaths from this disease. At present it occurs more commonly in females than males. The frequency of melanoma cases increases with age but an unusually high number of melanomas is observed among young people where almost a third of cases (31%) occur in people aged < 50 years. It is the commonest cancer type among 15-34 year olds.

Based on previous estimates, it is expected that almost 70,000 new cases of melanoma were diagnosed in Europe during 2010-11.

Further information

European Cancer Observatory: This site presents the number of cases and deaths by cancer in European countries and is updated regularly.

http://eu-cancer.iarc.fr/cancer-11-melanoma-of-skin.html,en

2.3. Aetiology of melanoma

There are several causes responsible for cutaneous melanoma and a number of risk factors have been identified such as:

- Ultraviolet light (UVR) exposure
- Sensitivity to sunlight (e.g. Type of skin, eye colour, hair colour, number of moles)
- Genetic factors
- Previous history of a skin cancer
- A weakened immune system (immunosuppression)

Ultraviolet exposure

Ultraviolet light exposure results in a number of changes which together result in a weakened protective system in the skin and an increased likelihood of developing a skin cancer. These changes include DNA mutations, increased production of growth factors which stimulate cell growth, reduced immunity, and formation of reactive oxygen species which are toxic and dangerous molecules for the skin. There is also evidence that intermittent, high intensity exposure to sunlight particularly during early life can result in an increased risk of developing melanoma. A history of sunburn also doubles the risk of developing melanoma, and the use of sun beds and sunlamps (an artificial source of sunlight used for tanning) also increases the risk of melanoma in young adults.

Sun sensitivity

Fair skin burns easily resulting in freckles and tans with difficulty. This type of skin, blue eyes, red hair and those individuals with a high number of moles are typical risk factors associated with melanoma.

Genetic factors

A family history of melanoma is a significant risk factor and an estimated 10% of all melanoma cases report a first- or second- degree relative with melanoma. In families where members have many cases of melanoma, the inheritance appears to be due to a single gene mutation. However, the majority of families show a complex pattern of inheritance suggesting melanoma, which probably occurs through the interaction between genetic and environmental factors. The genetic factors which predispose individuals to melanoma can be divided into high penetrance genes and low penetrance alleles.

- High penetrance melanoma susceptibility genes.

  These are mutations in the germline (i.e. in the lineage that in the body is responsible for reproduction and therefore when transmitted, a germline mutation is incorporated in every cell of the body, in contrast to a somatic mutation which is acquired in a single body cell). Germline mutations can be passed from parent to child. Germline mutations in the CDKN2A locus (40%) and cyclin-dependent kinase-4 (CDK4) (2%) are the only ones identified in melanoma. These are essential genes which regulate the cell cycle, therefore the speed of cell growth. Mutations of these genes make the cancer grow faster. In addition, the frequency of the CDKN2A mutations are influenced by sunlight exposure, demonstrating an important gene-environment interaction.

- Low penetrance melanoma susceptibility alleles

  Epidemiological studies have established that the risk of developing melanoma could also be directly related to pigmentation phenotype. Fair skin, poor tanning response, red or blonde hair and freckles are all known melanoma risk factors. Studies analyzing all genes in many different individuals have identified some genetic determinants of skin, hair and eye colour variation. A single nucleotide change (known as single nucleotide polymorphism) in some genes involved in the skin pigmentation pathway (melanocortin-1 receptor (MC1R), agouti stimulating protein (ASIP), tyrosinase (TYR) and tyrosinase-related protein-1 (TYRP1)) can increase susceptibility to melanoma. These are mutations that don’t occur frequently and are not inherited through the family.

Immunosuppression

A functional immune system is important to protect the body from melanoma; it is therefore expected that immune-suppressed patients (e.g. patients who have been receiving an organ transplant, need to reduce their immune-defense system in order to prevent a rejection reaction, or HIV patients who have a weakened immune system) would be at a greater risk

for developing melanoma. The immune system may be important in both the development and outcome of melanoma.

2.4. Diagnosis

The following features highly suggest that a skin lesion might be a melanoma:

- A new mole which is changing in shape, colour or size
- A longstanding mole which is changing in shape, colour or size
- Any mole which has three or more colours
- A mole which is itching or bleeding
- Any new persistent skin lesion especially if growing, if pigmented or red in appearance, and if the diagnosis is not clear
- A new pigmented line in a nail especially where there is also damage to the nail
- A lesion growing under a nail

Suspicious pigmented lesions need to be removed in their entirety (excision biopsy) and then analysed by a pathologist. The best outcome occurs when the correct diagnosis is made at an early stage which can result in earlier treatment.

- **ABCDE criteria:** In 1985, a group at New York University established the ABCDE criteria (Asymmetry, Border irregularity, Colour variegation, Diameter <6 mm, Evolution, which stands for change in size shape or colour over a short time) used as a simple tool to help to identify melanoma from a harmless mole. Others factors have been also taken into consideration such as inflammation (redness), crusting, or bleeding.
- **Dermoscopy:** Hand held microscopes (dermoscopy) have been used to increase the accuracy of making a diagnosis. These magnify the skin by 10-fold and help to identify structures in the skin such as dots, streaks, veils, and pigment networks usually undetectable by the naked eye. Changes in the pattern of these structures can help to determine if a mole is harmless or a more likely to be melanoma.

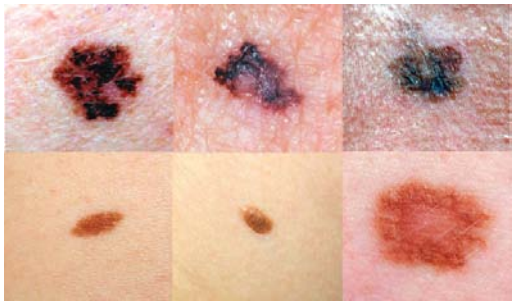

Fig. 1: Comparison of early melanoma (top) exhibiting the ABCDE features vs benign nevi (bottom)

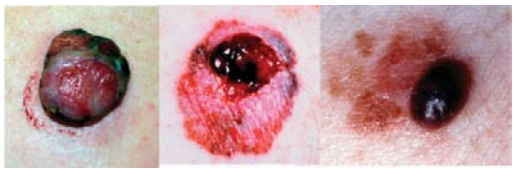

Fig. 2. Advanced melanomas demonstrate ulcerative and nodular presentations. All of these patients died within 1 year from when these images were recorded

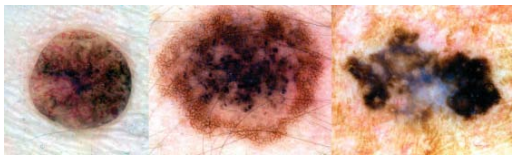

Fig. 3. Dermoscopic images of (left to right) a normal nevus, a dysplastic nevus, and a melanoma (note blue-white veil)

Credit for figs.1, 2 & 3: Rigel D. et al., CA Cancer J Clin 2010;60:301–316

2.5. Prognosis

The prognosis for melanoma is highly dependent on the stage it is at when it is found. If caught early, melanoma can be cured. The risk of the cancer coming back increases with the depth of the tumour - deeper tumours are more likely to come back. If the cancer has spread to lymph nodes, there is a greater chance that the melanoma will come back. When left untreated, it can and usually does spread (metastasize) to other organs in the body. The high rate of metastasis is the main reason melanoma is considered the deadliest skin cancer.
Overall, males diagnosed with melanoma have a 5-year survival of 78%, for females this is 91% (Cancer Research UK) but advanced disease has a worse prognosis with only 11% of individuals surviving 5-years. There are a few recognized features which determine the outcome for melanoma and predict recurrence and survival, including

a) Breslow thickness (the vertical thickness of the tumour when analysed under the microscope)
b) mitotic rate (the measure of the speed of cell growth in the dermis)
c) ulceration (as determined under the microscope)
d) the number of lymph nodes involved
e) if a patient is immunosuppressed.

2.6. Treatment

The first step in the treatment of melanoma is prevention. The best way to prevent melanoma is to avoid sunburn and reduce sun exposure in both children and adults. Just getting one bad, blistering, sunburn during childhood raises the risk of developing melanoma. Once melanoma has developed, treatment is tailored around a variety of factors, including the individual case, the type of melanoma and how much the melanoma has grown and spread.

Early detection of melanoma renders the disease curable in patients undergoing surgical excision. Treatment therefore involves complete surgical removal of the cancerous mole or area of skin. Local lymph nodes may be tested for the presence of cancer cells, indicating whether melanoma has spread. Additional surgery, chemotherapy, radio- and/or immuno-therapy may be needed if melanoma has spread beyond the skin to the lymph nodes and other parts of the body. For most patients where the melanoma has spread beyond the skin, there are no effective treatments and although many new treatments have been tested over the past 30 years, the survival rates for this disease have not changed much. The future is therefore to develop more effective treatments for this cancer.

Chemotherapy for melanoma

Chemotherapy uses anti-cancer drugs to destroy the growth of cancer cells. As they circulate in the blood, they can reach cancer cells wherever they are in the body. Chemotherapy may be used for an advanced melanoma that has spread to another part of the body (metastatic disease). There are several newer types of chemotherapy and combinations of drugs being evaluated in clinical trials both for metastatic disease and as an additional treatment for people with local lymph node spread. In addition, the combination of chemotherapy and anti-angiogenesis inhibitors (substances that prevent the formation of new blood vessels that tumours need to grow and spread) or immunotherapy is also being explored.

Side effects

Different drugs have different side effects. Some common side effects of chemotherapy include a drop in the number of blood cells, feeling sick, diarrhoea, hair loss or thinning, sore mouth, feeling tired, and loss of fertility.

Radiotherapy for melanoma

Radiotherapy uses high energy rays to kill cancer cells. Radiotherapy could be used for advanced melanoma, to shrink the tumours and help control symptoms, for example when melanoma has spread to the brain or bones.

Side effects

The side effects will vary depending on which part of the body has been treated. Radiotherapy just to the skin does not have very many side effects. The skin may become slightly red and sore.

Biological therapy for melanoma

Biological therapies are treatments that use substances naturally produced by the body. Some of these treatments are called immunotherapy as the drugs stimulate the immune system. The most common immunotherapy used to treat melanoma is interferon. Interferon helps the body attack cells that the body recognises as abnormal, for example cancer cells. Interferon treatment has been tested in melanoma for some years. But it is still an experimental treatment and has not been proven to help cure melanoma.

Currently, melanoma vaccines are being intensely evaluated in clinical trials for patients with both localized and advanced melanoma. The vaccines are made using certain proteins found only on a melanoma tumour and are given as an injection; the person's immune system then recognizes the proteins and destroys melanoma cancer cells.

An example, ipiluminab is a promising new experimental immunotherapy for the treatment of patients with melanoma. Ipiluminab is a monoclonal antibody directed against CTLA-4 (cytotoxic T-lymphocyte associated molecule-4). This new approach works by taking the brakes off the immune system. Ongoing clinical trials of ipiluminab for patients with advanced melanoma will provide further guidance regarding the role of this drug in the treatment of melanoma.

Side effects

In particular the immunotherapy could eventually trigger "autoimmune" side effects in which the patient's own immune system attacks normal cells in their body.

Targeted therapy

Targeted therapy is a treatment that targets specific genes or proteins. It is a major area of research for melanoma. Ongoing research has identified a number of molecular pathways and activated or mutated genes in melanoma. This includes the most commonly mutated gene BRAF as well as activation of the MAP kinase pathway. Ongoing laboratory and clinical research confirms the importance of these genes and pathways in melanoma.

There are several drugs in development that target BRAF and the MAP kinase pathway. This includes BRAF inhibitors (PLX4032, also known as RO5185426), GSK BRAF inhibitors, and MEK inhibitors. There are many ongoing clinical trials exploring these new approaches. Ongoing clinical trials are evaluating the optimum dose and schedule and combining targeted therapies with other pathway inhibitors, as well as combining these therapies with immunotherapy. Another important focus is the development of agents which target the C-kit

gene, which is mutated or associated with extra copies of the gene in certain subtypes of melanoma including lentigo maligna melanoma, mucosal melanoma, and acral lentiginous melanoma (melanoma of the palms, soles, and nail beds).

2.7. Molecular pathways

Genes involved in the development of melanoma are critical to maintain cell proliferation, differentiation and apoptosis (cell death). It is thought that some melanomas arise from melanocytes or from harmless moles. There is evidence that a specific combination of changes and abnormalities in genes from these different pathways can result in the development of melanoma. Among the main forces limiting the ability of melanoma cells to die to their appropriate and physiological levels and promoting an uncontrolled mechanism of cell proliferation and survival are the Raf/MAPK pathways. These signaling cascades are organized in intricate networks, and multiple genetic alterations of them occur in melanoma, including mutations that activate Ras and two of its effectors cascades, Raf and phosphoinositide 3-kinase (PI3K).

Here we highlight the most studied molecular targets in melanoma:

MAPK (mitogen-activated protein kinase): MAPKs are a family of enzymes that form an integrated network influencing cellular functions such as differentiation, proliferation, and cell death. These cytoplasmic proteins modulate the activities of other intracellular proteins by adding phosphate groups to their serine/threonine amino acids.

BRAF: BRAF is an isoform of RAF. Raf proteins (Raf-1, A-Raf, B-Raf) are intermediate to RAS and MAPK in the cellular proliferative pathway. Raf proteins are typically activated by RAS via phosphorylation, and activated Raf proteins in turn activate MAPK via phosphorylation. However, Raf proteins may also be independently activated by other kinases.

RAS: The RAS gene family consists of H-RAS, N-RAS, and K-RAS. The RAS proteins are typically small triphosphate-binding proteins, and are the common upstream molecule of several signaling pathways that play a key role in signal transduction, which results in cellular proliferation and transformation.

MITF: Microphthalmia-associated transcription factor is an early marker for melanocyte lineage and essential for normal melanocyte development. It induces transcription of genes important for melanin production, including tyrosinase. Currently, there is contradictory data regarding MITF, both supporting and negating a role in melanomagenesis.

2.8. Animal models

A wide variety of animal models of malignant melanoma are currently available to researchers who are interested in the process of this disease: including Sinclair swine and Camargue horses. Although neither example generates melanoma with a sunlight aetiology the swine represents an interesting model, as the skin of the pig resembles the structure of the human skin. Angora goats, develops in response to a chronic sunlight exposure, lentiginous melanoma comparable to a form of melanoma described in the elderly.

More accessible to experimentation, however, are the non-mammalian Xiphophorus fish model and the marsupial opossum, Monodelphis domestica both of which develop melanomas in response of UV exposure and which spontaneously metastasize to other organs. Melanomas arise spontaneously in dogs, and this model has been used to evaluate novel cytokine combinations and gene-therapy protocols.

The most exploited model for studying melanomas is the mouse one, also due to the increasing understanding of mouse genetics. Melanomas initiation in mice is not a spontaneous event therefore induction of it is obtained via application of physical agents or specific genetic manipulations (transgenic mice) as well as the inoculation of mice with tumour-cell lines.

These models have the advantage of an intact immune system, which allows the investigators to study not only the molecular events within the tumours, but also to look into the immune responses against these tumours.

Finally, the more recently described models which employ immunodeficient mice (SCID) provide a method for studying human tumours under controlled conditions. These mice have been genetically manipulated in order to compromise the immuno-response and allow injection or incorporation of material from human origin without any rejection problem. For example these models allow injection under the skin or into the tail vein of cells isolated from human metastatic tumours. Although the incidence of spontaneous metastasis from primary tumours to other organs is pretty low, tumorigenicity (tumour formation) can be established few weeks later by quantitative measure of lung colonies (number of tumours aggregate in the lung, typically one of the primary targets of metastatic melanoma cells).

2.9. Clinical trials

A new treatment for melanoma is showing promising results in patients with a particular gene mutation. In a study recently published in the New England Journal of Medicine, patients with metastatic melanoma were treated orally with a drug called PLX4032, which targets a gene mutation (BRAFV600E) associated with an increased risk of melanoma. Abnormal changes in what is known as the BRAF gene are found in 40-60% of all melanomas. Mutated versions of BRAF can become stuck in the “on” position, promoting uncontrolled (cancerous) growth. PLX4032 is a novel BRAF “inhibitor” that can slow or even halt this growth. In a group of 32 metastatic melanoma patients with the BRAF mutation, PLX4032 resulted in tumour shrinking in 81% patients. Responses have lasted anywhere from 2-18 months. It is not yet clear whether treatment with PLX4032 will lead to improved overall melanoma survival rates, but the authors are currently investigating this in a larger trial. Around 30% of the patients treated with PLX4032 developed squamous cell carcinomas (a milder form of skin cancer).

PLX4032 provides the first evidence that therapy targeting tumours containing activating BRAF-V600E mutations can significantly reduce tumour size in melanoma. This is the first example of successful targeting of an intracellular signaling molecule which has an activating mutation. Although there has been impressive success with the selective kinase-targeted therapies, the long-term outcome is still awaited. Initially treatment-responsive patients ultimately develop resistance to the treatment and relapse. By understanding how this occurs a rational basis for combination therapy or second-generation drugs may then be developed to combat this resistance.

Further information:

GenoMel is an international research consortium. Their website includes interactive resources about melanoma. http://www.genomel.org/index.php

http://www.genomel.org/patient_information.php

3. Ethical, Legal and Social Aspects (ELSA)

In this section you will find a number of opinions and incentives for discussion in class on ethical, legal and social aspects (ELSA) related to skin cancer:

3.1. Introduction

Melanoma is a common cancer, and one that is reasonably well known to the public. But this familiarity can be misleading: it may not be taken as seriously as other cancers, because it is thought to be easily treatable, and because people may think of melanomas as being little different from harmless moles until it is perhaps too late. Prevention, early detection, and early treatment are crucial, but this may not be well understood, particularly in countries, like the UK, where sunshine is thought to be entirely beneficial and relatively unusual, where tans are fashionable, and where sunburn is discussed with amusement!

3.2. Prevention

Prevention of melanomas is a public health issue. Public education campaigns about the risks of intermittent, high intensity exposure to ultraviolet radiation, particularly sunlight and artificial ultraviolet light in sunbeds, can make a significant difference to people's awareness of the risks, and to their behaviour. Public awareness of the risks of sunburn and overuse of sunbeds is relatively low, as is the public understanding of the efficacy of preventive measures such as covering up, use of suncreams and sunblocks, UV filtering glass in windows, and so on. The marketing and sale of suncreams and sunblocks with reference to "sun protection factors" is neither especially clear, nor is the evidence-base (if any) underlying these indices ever explained to the public, and although more publicity has been given to how best to apply creams, how long their protective effect lasts, and how it is modified by sweat or bathing, this is again not well grasped by most users.

There has been some recent controversy about the safety of sunbed use, and calls for tighter regulation of this industry, especially where the clients are under 18 years of age. But the regulation of the industry is not risk-based. Overall, while a "healthy tan" remains fashionable, there will be significant public communication difficulties about the need to be sensible in the sun. And focussing on the risks of UV exposure can be controversial and counterproductive in light of people's enjoyment of outdoor work and leisure, and the known health benefits.

So far as biomedical prevention is concerned, there are no genetic tests that are sensitive and specific enough to guide clinical decision-making, preventive strategies, or reproductive choices. But in future it may be possible to give advice to would-be parents who have family histories of melanoma: this would be subject to the usual ethical worries about the use and abuse of genetic tests in reproductive medicine. It might also be possible to use medical interventions that are protective against the effects of genes known to be involved in biological pathways that lead to melanoma formation. There would then be an ethical debate about the relative merits of pharmaceutical prevention and behaviour change. However, this type of treatment might be especially useful in patients at high risk of melanoma (in particular, those who are immunosuppressed).

A final consideration in terms of prevention concerns the impact of environmental change. Climate change and ozone layer depletion are having a significant impact in terms of people's exposure to harmful levels of UV radiation. The Australian experience of rising melanoma rates due to the Ozone hole, high summer temperatures, and a highly outdoor-oriented culture is illustrative here. But it also illustrates the effects of widespread culture change ("Slip on a T-shirt, slop on the suncream, slap on a hat" and a change in attitudes to sunburn from amusement to disapproval), in combination with early diagnosis (through primary care screening and patient self-monitoring) and treatment in reducing melanoma incidence.

3.3. Diagnosis and screening

The first step in diagnosis will normally lie with the patient coming forward to her GP with a concern. Physician-initiated screening will be relatively unusual except in high-incidence countries or in specific high risk-groups (such as the immuno-suppressed): the normal considerations of effectiveness and cost-effectiveness will control how and when a screening programme could be initiated. Since the consequences of a false positive in primary care treatment or referral are relatively minor (mild anxiety in the patient and very minor physical discomfort during and for a short while after biopsy), the main concern here will normally be with avoiding false negatives in patients who do present with a mole or skin lesion of concern to them, and with encouraging patients to present and not to ignore what may be warning signs of melanoma.

However, the best ways to encourage patients to seek diagnosis are not entirely clear, and the benefits must be traded off against the costs in terms of resources diverted from other

uses, and against the adverse consequences in terms of health behaviour of inducing excessive anxiety or caution.

Although false positives may be of relatively little concern from a medical point of view, from a public health point of view they could become quite costly if they were relatively frequent, and undermine the confidence of the public in the reliability and utility of seeking diagnosis, and the quality of clinical care more generally. This speaks to a need to ensure that diagnostic criteria are simple, robust, easy to validate, and useable by non-specialists – who must also have access to appropriate training. Similar remarks apply to the development of patient/user tests of the checklist or home diagnostics type. While tests that can usefully encourage patients to seek professional advice can be beneficial, medical devices and testing kits could be quite damaging if unreliable, hard to interpret, or understood to be definitive, clinical grade, testing protocols.

The most serious difficulty in fact may be the usual problem in healthcare that patients who could benefit from screening, diagnosis or treatment fail to come forward – and for many years it has been known that people's willingness to seek medical help is lower in poorer socioeconomic groups, for various reasons. If melanoma is also commoner in poorer socioeconomic groups, this can lead to significant health inequalities and healthcare provision inequities.

3.4. Treatment

The ethical challenges of treatment are perhaps better understood than those of treatment: good communication is the key, so that the patient and their family understand the nature of the illness, the treatment options and their associated risks and benefits, and the likely prognosis. In some cultural groups there may be less willingness to disclose a cancer diagnosis to the patient herself, but this may be less difficult in the case of melanoma (at least in its early stages) once it is understood that it is usually a highly treatable illness. Patients (or their families) may focus on the word "cancer" and become fatalistic or decline treatment or disclosure of diagnosis. Yet the treatment would under normal circumstances be very highly effective.

The two main difficult issues relating to treatment are availability and research. In advanced disease, where available treatments are rather ineffective, rather costly, or both, there can be serious difficulties in terms of the affordability and cost-effectiveness of treatment. Therefore there can be difficult judgements for commissioners of treatment about whether to offer particular courses of treatment – or for clinicians, about whether to disclose that a course of

treatment may exist but which the NHS or private provider will not pay for. These decisions about cost-effectiveness, be they made in general terms by the National Institute of Health and Clinical Excellence (NICE) or specifically by doctors or primary care trusts (or their successors), are hard to challenge.

3.5. Research

There are significant open questions relating to the design and evaluation of health promotion and health education programmes in melanoma. The same applies to the evaluation of preventive strategies, especially those involving products (such as creams) that are more the province of the cosmetic, than the pharmaceutical, industry. Given the importance of prevention in controlling melanoma, this points to a serious ethical problem relating to the proper allocation of resources for research. And as with any medical or quasi-medical product, it may require a significant regulatory push to force the industries in question to subject their products to appropriate, unbiased testing, and to ensure that the information they use to promote their product and guide users is reliable, accurate and open to verification.

The ethics of research into treatments is much better understood, since the regulatory system for drugs and devices is very much better developed and subject to clear guidelines and principles. This is true both in animal and human subjects research. Although controversy does stalk both animal research in dermatology (particularly in the case of use of genetically modified animals as model animals in cancer research) and healthy volunteer studies in humans (there was a long period in which prisoners were prime subjects for dermatological research, in the US particularly), the guidelines and supervision of such research are broadly robust and respected.

Some difficulties may arise in clinical trials proper (Phase II and III studies involving patients). In particular, some patients may find it impossible to get a treatment unless it is in a clinical trial (even if it is a licensed product), on cost grounds – yet being in a clinical trial may mean assignment (by randomisation or otherwise) to the control group anyway. Since no research study is entirely without risk, it may be that some people are almost coerced into taking such risks simply because they have no other way of accessing the drug their clinician believes that they need.

Other problems, relating to consent, can arise: one such is the therapeutic misconception, such that the patient believes that they are getting “the best treatment for my disease” when the clinician is actually enrolling research participants precisely because he doesn’t know

what is the best treatment for the disease, and allocation to a treatment may have nothing to do with the specifics of any individual patient (obviously so, when allocation is randomised). Patients may also believe that the experimental treatment is by definition the best treatment, simply because it is the most up to date. Equally, some patients may seek to cheat the protocol or to go overseas to destinations where the treatment is available outside any trial protocol, at great expense and, sometimes, great risk (both from the untested treatment and from unscrupulous or otherwise poor quality care in the destination clinic and after).

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