"The State of Melanoma: Challenges and Opportunities"
Executive Summary

In late 2015, the Melanoma Research Foundation (MRF) convened of summit of internationally-renowned melanoma experts for an in-depth discussion on the current understanding of, and future recommendations for, melanoma research. The result of the comprehensive process is a new white paper entitled, "The State of Melanoma: Challenges and Opportunities," published in the latest edition of the highly regarded journal, *Pigment Cell & Melanoma Research*. In the white paper, the melanoma experts, including researchers, clinicians and patient advocates, identify the current status, challenges and opportunities in four respective areas: prevention, detection and early diagnosis, dormancy, early metastasis and therapy.

Key Takeaways:

The white paper includes a roadmap that outlines the challenges and opportunities across the melanoma landscape:

- Proper use of sunscreen can reduce incidence of melanoma by up to 50%. Current sunscreens block portions of both UVA and UVB, but not everything within those bands. More research needs to be done about what range of wavelengths in the UV band needs to be blocked.
- Melanoma cells have demonstrated the ability to remain dormant in the body for many years—even decades. Understanding how these cells can survive and what causes them to awaken and progress is a vital component to melanoma treatment.
- Currently 25 biopsies are performed for every melanoma found. Given the incidence of melanoma, and a demonstrated 40-70% underreporting rate, this translates to more than 4 million biopsies performed to diagnose 170,000 melanomas. Developing more precise methods of diagnosis will result in less trauma for patients and significantly reduced healthcare costs.
- Clinicians are seeing resistance to immunotherapy develop after an initial positive response. Identifying how acquired resistance happens—whether with targeted therapy or immunotherapy—and how to overcome resistance is essential in maximizing the benefit of these treatments.

A more detailed comprehensive summary of the white paper can be found here.

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"The State of Melanoma: Challenges and Opportunities"
A Detailed Summary of Key Findings

Melanoma is, by far, the deadliest form of skin cancer, resulting in nearly 10,000 deaths in the United States every year. Some unique characteristics of melanoma make preventing and treating this cancer particularly challenging, yet those same characteristics also offer some intriguing opportunities. Perhaps the most obvious is that melanoma mostly begins on the skin—the only bodily organ that is readily visible and accessible. In addition:

- Rates of melanoma continue to rise in almost every country—including the United States. The cause of most of these melanomas, however, is clearly exposure to UV radiation from the sun or tanning beds. This knowledge offers the opportunity to create programs around awareness and early detection that can lower melanoma rates.
- Melanoma has more mutations than any other cancer. This makes it remarkably nimble at surviving treatment. In contrast, the fact that it is so heavily mutated makes engaging the immune system to attack melanoma cells more effective.
- A large percentage of melanomas have a known "driver" genetic mutation—BRAF—that can be blocked with drugs currently available, but the median response time to these drugs remains relatively short.

Progress toward treating melanoma has been remarkable over the past few years. Still, until a number of critical questions are answered the incidence and mortality of melanoma is likely to increase. With that in mind, the Melanoma Research Foundation (MRF) convened a group of leading experts to focus on four primary topics: prevention; detection and early diagnosis; dormancy and early metastasis, and therapy. Each sub-group was charged with providing a survey of current understandings and then to reach consensus on specific recommendations for the focus of future research. The following is a summary of their work.

PREVENTION

Skin cancer, including melanoma, is one of the most preventable cancers. Despite this, incidence of melanoma continues to rise or, at best, remain stable. More research is needed across the board to make prevention efforts more impactful.

<u>Why do some people develop skin cancer and others don't?</u>

The vast majority of skin cancers are caused by UV radiation. Many people tan extensively and never develop skin cancer, while others who rarely tan are diagnosed with skin cancer. This suggests that while UV is the cause of these cancers, other factors are significant in whether UV exposure will lead to malignancy.

Some risk factors are unique to the individual—genetic makeup, the ability to tan and the body's capacity to repair damaged DNA all play a role. Others are environmental and relate to how much UV radiation is received, how often, and at what stage of life. Childhood sunburns and the use of tanning beds in the teen years significantly increase the likelihood of having melanoma. More research is needed in understanding the role of different bands of UV radiation (UVA vs. UVB) in cancer risk. Too, little is known about the precise impact of skin pigmentation on

susceptibility. Greater understanding of these factors could be used to shape more targeted and effective prevention strategies.

How can we incorporate what we know about the role of genetics, diet, and behavior into the clinical process of evaluating suspicious moles?

Researchers have demonstrated that people with light eye and hair color, and people with a lot of moles, are more likely to develop melanoma, but no-one has studied relative risk for different types of melanoma. Some sun-related melanomas show signs of long-term UV exposure, with chronic sun-damaged skin and a large number of genetic mutations. Others reflect intermittent sun exposure. These have fewer mutations, but often have the common “driver” mutation of BRAF. How do known risk factors impact the likelihood of developing melanoma from these two kinds of sun exposure?

Some melanomas are not related to UV exposure at all. What characteristics, if any, suggest elevated risk and justify more aggressive monitoring? What is the role of diet? Of environment? Of genetic make-up? Bringing the findings of the afore-mentioned factors into the clinical evaluation process is critical, but changing clinical practice requires data that is not currently available.

What portions of UV radiation need to be blocked by sunscreens? How effective must sunscreens be in order to lower the risk of melanoma?

Proper use of sunscreen can reduce incidence of melanoma by up to 50%, but little is known about what range of wavelengths in the UV band needs to be blocked. Should we be focusing more on UVA or on UVB? What segments of UVA or UVB? Current sunscreens block portions of both UVA and UVB, but not everything within those bands. Would blocking a wider range of radiation be a better strategy?

And, how effective do these filters, or blocking agents, need to be? Do more effective UV filters enhance efficacy? Research uncovering this information will help shape effective prevention strategies.

What are the conscious and subconscious motivations that cause people to engage in risky sun exposure?

Recent studies have shown that risk-behavior around UV exposure is related to both positive and negative messages. Frequent tanners report that tanning makes them feel better, makes them feel more attractive, and helps them fit in with their peers. Tanners also report using tanning to self-treat fatigue and depression.

Researchers need working models that can be used to understand how and why these motivations are important and how they play out in various age and social groups.

What is the best communication strategy to change the sun safety behavior of at-risk groups of people?

With enhanced understanding of risk-behavior comes the opportunity to develop messages that will lead to behavior change. Since different groups will likely respond to different kinds of messages, based on their motivations and behavior patterns, targeted communication is essential. Sun-seeking behavior is almost certainly addictive, at least in some groups. In addition, such behavior may be driven by an evolutionary pathway, dating to a time when sun exposure was essential to developing vitamin D. Creative approaches are essential to overcoming those subconscious drivers of risky activity.

Can we develop chemicals and drugs that will block or repair the damage caused by UV exposure?

Finding natural and/or safe products to prevent cancer has been the subject of great interest for several years. The biology of cutaneous melanoma makes it uniquely suited for approaches in which individuals at high melanoma risk are treated with safe drugs or natural products that may prevent or reverse melanoma development. We know key pathways in tumor cells that drive their growth, and can monitor activation of those pathways. We know that the appearance of new, benign moles indicates activity that can signal melanoma development, and because cutaneous melanoma is on the skin, researchers can take a series of biopsies to track changes.

Currently no proposed chemoprevention agent has proven successful in stopping melanoma. In contrast, some data suggests that anti-oxidants—long-touted as being a protector against cancer—may in fact promote cancer, including melanoma. With increasing ability to identify high-risk individuals, this avenue of exploration has become increasingly important.

Research is needed to identify drugs that can stop melanoma formation. Drugs already tested for treating melanoma need further evaluation for their potential in prevention. And, these drugs need to be evaluated in the context of high-risk individuals so as to maximize the risk/benefit ration.

Can bacteria in the gut play a role in reducing risk of melanoma?

Increasing evidence is linking the presence of certain gut bacteria to resistance to melanoma development and to response to treatment. These studies are provocative, but as the influence of the gut microbiome is in its infancy, more work must be done to validate and expand current findings. With this knowledge, individuals may be able to alter the composition of bacteria in the gut so as to lower risk and improve response to therapy.

DETECTION/EARLY DIAGNOSIS

In recent years great advances have been made in understanding the basic mechanisms driving the formation of the various subtypes of melanoma, yet the primary tools for detection and early diagnosis have remained relatively unchanged for several decades. Incorporating the scientific advances into the clinical setting may increase the accuracy of early detection, thus lowering healthcare costs and resulting in better outcomes for patients.

How can we diagnose melanoma earlier?

Melanoma is ultimately diagnosed through pathology, but wide variation—as much as 15%—exists among pathologists in distinguishing between a benign nevus and melanoma. Current studies are evaluating various means of testing genetic variation and mutation as a more precise diagnostic approach, but these tests need further evaluation and validation so as to provide accurate, cost-effective and practical methods for improving the diagnosis of melanoma.

How can we be better at determining which lesions are likely to mutate and become active melanoma?

Melanomas begin with precursor lesions, some of which are present in a benign state for years. Research is needed to understand how and why these precursors become active. This work should be done across the various types of melanoma. The identification of clinical, molecular or immune markers of risk will improve diagnosis, prognosis, and appropriate early intervention.

Can we find early recognition systems for various sub-types of melanoma?

Melanoma consists of several subtypes, with different mechanisms driving the cancer. Despite the advances in understanding these subtypes, current early recognition algorithms (ABCDE) apply only to certain forms of melanoma. Similar approaches need to be developed for other subtypes in order to advance early detection.

Research is needed to improve staging for melanoma sub-types.

Similar to above, current staging criteria are largely based on more common forms of melanoma. More recent discoveries about other molecular subtypes need to be incorporated into staging criteria. This will improve current guidance around the likelihood of recurrence or metastasis. Such knowledge may also improve our ability to predict the likely ultimate outcome of disease.

Research is needed to find more accurate, less costly methods of diagnosing melanoma.

Currently 25 biopsies are performed for every melanoma found. Given the incidence of melanoma, and a demonstrated 40-70% underreporting rate, this translates to more than 4 million biopsies performed to diagnose 170,000 melanomas. Developing more precise methods of diagnosis will result in less trauma for patients and significantly reduced healthcare costs.

How can we use digital imaging and other technologies to evaluate and track skin lesions?

Digital imaging and other non-invasive technologies are emerging as promising approaches to evaluating and tracking skin lesions. Assessing outcomes and finding standard best practices across the multiple developing platforms is critical if this approach is to achieve wide-spread adoption. Similarly, more than 100 consumer-focused mobile phone apps have been developed, yet little data exists supporting the validity of these tools.

Media campaigns can be effective in changing sun protection behavior and increasing routine screening. Research is needed to shape common messages and strategies that are proven to work.

Media campaigns have been launched in various countries focusing on sun protection and/or routine screening. The largest and most well-known is Australia's "Slip, Slop, Slap" campaign that has arguably resulted in measurable reduction of melanoma in that country. Most campaigns, however, are developed in isolation from other similar efforts and with little opportunity for evaluation of effectiveness.

Developing common messages on prevention and common protocols for screening is critical to evaluating the relative value of these programs. Any media campaigns, whether for prevention or early detection, should be designed with best practices for healthcare communication in mind, and in such a way that data regarding impact can be collected. These campaigns need more wide-spread promotion, but also should be tested for measurable changes in behavior.

DORMANCY AND EARLY METASTASIS

Melanoma cells have demonstrated the ability to remain dormant in the body for many years—even decades. Understanding how these cells can survive and what causes them to awaken and progress is a vital component to melanoma treatment. This issue can be divided into three factors: the ability of melanoma cells to become dormant; the ability to sustain dormancy over a long period of time; and, the ability to re-awaken with the capacity to create new tumors.

How can we catch metastasis earlier, when it is more treatable?

When a patient is several years out from any evidence of cancer, scans are done less often, if at all. This means that patients whose melanoma has been dormant for a long period are often diagnosed with recurrence late in the disease progression. Current work is evaluating the use of circulating tumor cells and/or circulating tumor DNA as a method of determining metastasis. These studies need additional support and other evaluations, such as determining if tumor cells can "hide" in bone marrow. This effort could result in non-invasive, cost-effective ways to determine if dormant cells have awakened and are proliferating.

What allows melanoma cells to become dormant? What is required by the cell to still be viable in this condition?

Little is known about how melanoma cells become dormant. Research is needed to determine what is required for the cells to be protected for long periods of time. Do cells find safe havens in certain kinds of tissue or in bone marrow, from which they can later escape? If so, what about those spaces keeps the cell dormant, but viable? Could certain cancer treatments actually drive tumor cells into dormancy?

What enables dormant cells to retain the ability to form new tumors?

Dormant melanoma cells clearly retain the capacity to awaken and form new tumors, but the mechanism by which cells maintain that ability is not known. Likely a balance is maintained in

which new cells are being formed and old ones are dying but at a very low rate. This parallel control of cell growth and cell death is likely driven by a combination of signals from within the cell and from the surrounding microenvironment. Understanding these signaling patterns is essential to addressing dormancy.

Genetic models are needed in order to study dormancy, and to understand how cells awaken from dormancy.

In order to understand how dormancy happens and how cells awake from dormancy, researchers must develop animal models with melanoma that copy what happens in the human body. Such models, likely in mice or zebrafish, must meet a number of requirements, including: the ability to metastasize; having an intact immune system; being able to switch dormancy on and off. The ability to evaluate the microenvironment of metastases is critical, as is live imaging of the tumor and whole body scans for the growth of blood vessels and lymph systems in response to tumor.

Do dormant cells need to be "awakened" by doctors in order to treat them successfully?

Treating dormant cells is very difficult. In the dormant state cells are not active enough to take up cytotoxic chemotherapies or targeted therapies, and they have the ability to hide from the immune system. Lowering the risk of future metastases from these dormant cells may involve waking the cells from dormancy so they become vulnerable to current therapeutic approaches. Doing so requires identifying pathways by which cells can be stimulated out of dormancy. Moreover, this approach raises significant ethical issues around causing cancer growth and risk of creating highly aggressive cancer cells.

Analysis should be done comparing tissue from patients who have had and who have not had metastasis after long periods of being cancer free.

Retrospective and prospective studies should be done using patients, particularly those in randomized clinical trials. One rational approach is to compare groups of patients with similar initial clinical profiles—e.g., thin melanomas and sentinel node involvement—but with different clinical outcomes. Analyzing samples collected as part of the trial process may reveal factors that predict outcomes, including the likelihood of future metastatic involvement. Such studies are best done collaboratively across many institutions and as a co-study conducted in parallel with a clinical trial.

Current clinical trials should be expanded to monitor for dormancy and metastasis, using biomarkers and "driver" mutations.

A large percentage of melanoma patients are cured through surgery. The cure may be related to surgery removing all cells, or may be due to the lack of dormant cells in that patient. Mechanisms for dormancy may differ at varying points of disease progression. Studies should evaluate dormancy at detection, at progression, and during treatment. Such an evaluation may uncover ways to block the awakening process, particularly in patients with earlier disease. Doing so will require developing blood-based biomarkers and new imaging strategies that can detect and indicate the status of dormant cells.

THERAPY: STATUS, CHALLENGES, AND OPPORTUNITIES

The melanoma treatment landscape has changed radically in recent years, with breakthroughs in research driving the shift from having no approved therapies with demonstrated overall survival benefit to 10 new therapeutic regimens in the brief span of 2011 to 2015. Much is unknown about these new drugs, however, including how to sequence and/or combine available treatments, how to address acquired resistance to therapy, and which drug is likely to work best with which patient. Too, even with the best results of the current approved approaches more than half of patients with metastatic melanoma will have poor outcomes. The gains in recent years provide a robust foundation on which to address these outstanding questions.

Research is needed to uncover why some patients respond the therapy, but then stop responding.

Targeted therapy (treatments that interrupt the activity of a mutation inside tumor cells) has been characterized by high percentages of patients responding, and those responses happening quickly. Most patients only respond, however, for 12 to 15 months. In contrast, immunotherapy has lower response rates but a higher percentage of patients experiencing long-term responses. More recently clinicians are seeing resistance to immunotherapy develop after an initial positive response. Identifying how acquired resistance happens—whether with targeted therapy or immunotherapy—and how to overcome resistance is essential in maximizing the benefit of these treatments.

How can we best address the ongoing changes that happen in a tumor, which may lead to the tumor becoming resistant to treatment?

The mutation process that led to the formation of cancer does not stop with diagnosis. Rather, the tumor cells continue to evolve and change, leading to a collection of tumors and/or cell clusters with different genetic profiles within a single patient. Some cells in a given tumor may respond to a given drug, while others may have a different mutation that allows them to resist that drug. As the vulnerable cells die off, the resistant cells may then grow and become dominant.

Monitoring this phenomena—tumor heterogeneity—is important to evaluating what is happening during treatment. Typically heterogeneity has been found through biopsy, but this is not a realistic approach when ongoing tracking is needed. Research is needed to develop non-invasive tools (e.g., blood-based biomarkers or imaging for early response and resistance) to evaluate when and if cells are escaping therapy. Such tools could enable clinicians to measure ongoing response to therapy and make needed adjustments in more timely fashion currently afforded by scans or biopsy.

We need good models for various sub-types of melanoma that will help guide discovery of new, effective treatments.

Despite recent treatment progress, additional therapies are needed to address patients who do not respond to current therapies, and patients who have sub-types of melanoma that do not respond well to current available drugs. Effective animal models of these sub-types must be

developed in order to understand and accelerate new treatment options. Such models must replicate the genetic, immunologic, and biologic characteristics of the disease as it appears in patients.

What is the best strategy for treating patients who have stopped responding to the first line of therapy?

Progress in the initial treatment of patients has been dramatic, but has not been accompanied by similar advances in determining how best to treat patients who progress on first-line therapy. Particularly in targeted therapy, given the multiple mechanisms of acquired resistance, research is needed to develop biomarkers that will guide second-line therapies for each patient in this population.

Research is needed to improve the effectiveness and safety of immunotherapy drugs, and to determine who is likely to respond to these drugs.

Drugs that re-engage the immune system in fighting cancer have been proven effective in melanoma. The current strategy involves "checkpoint inhibition" or blocking the natural braking mechanism that stops the immune system's T-cells from functioning. Despite these advances, most patients do not have a complete response to these drugs, and checkpoint inhibition often entails significant side effects. More research is needed to improve the efficacy, safety, and tolerability of existing immunotherapy regimens while identifying new targets for drug development.

How can we better predict which drug combination(s) is best for a given patient?

Combining two or more drugs has proven beneficial, both with targeted therapy and immunotherapy. Little is known, however, regarding which combinations are optimal, the proper sequencing and dosing of drugs used in combination, which subsets of patients are likely to benefit from various combinations, and the potential of combining targeted therapy with immunotherapy. These trials need to be done in order to provide the best, most customized therapeutic approach for every patient.

Research is needed to find drugs that are effective for patients who have less-common genetic mutations driving their melanoma.

Currently the only approved targeted therapy is for patients who have BRAF V660e mutation, about half of the melanoma patient population. Research to identify effective targeted therapy approaches for other sub-populations who do not have this mutation is a critical unmet need. In addition to the above, research is needed in the following three areas:

- Should we give treatment to patients before they have surgery? Such treatment might shrink the tumor and make surgery easier. It might also reduce the likelihood of metastasis.
- What is the proper way to treat patients who have multiple occurrences tumors in or below the skin in the vicinity of the original melanoma? Should they be treated the same as a patient who has metastases in distant parts of the body or in other organs?

- We know that some patients respond to a given therapy remarkably well. How can we learn what distinguishes these “super-responders” from other patients? Can that information provide better guidance on how to use current drugs?

CLOSING COMMENTS

Underlying all of the above is the need to encourage participation in clinical trials, despite the availability of approved drugs. These studies are the best path forward to understand how to use currently available drugs and to develop new drugs. The way clinical trials are designed and conducted is important, and new models may need to be developed. In particular, trials should:

- Include specimen collection, conducted under common operating procedures so proper translational (bench to bedside) research can be done.
- Explore surrogate markers for success rather than relying simply on overall survival. Other markers such as seeing tumors shrink or disappear, stopping progression of disease, improved quality of life can allow for faster development at lower cost.
- Be conducted collaboratively across multiple institutions so as to reduce duplication of efforts and competition for patients to enroll in trials.
- Utilize a multidisciplinary team approach leverage synergies across disciplines.

The progress made in understanding and treating melanoma over the past few years has been remarkable. With such progress comes some new challenges. Having several approved treatment regimens may lead to complacency or hubris. We must remember that more than half of all patients with advanced melanoma will not survive their cancer.

The availability of approved drugs also makes enrolling patients in clinical trials more challenging. And we are seeing a proliferation of trials, many of which offer little hope of advancing our understanding of the field. The combination of more studies, but fewer patients interested in those studies threatens to slow down progress.

Finally, the melanoma field has benefited immensely by being highly collaborative. The increased interest in melanoma may change that dynamic, particularly as researchers seek to distinguish themselves in the field and as clinicians compete for patients.

It is our hope that the findings of this State of Melanoma meeting will help provide some clarity and direction to researchers. By focusing on the research priorities identified in the meeting the field can unite in a few key common efforts and work together to ensure that recent progress will continue until melanoma becomes a curable or chronic disease.