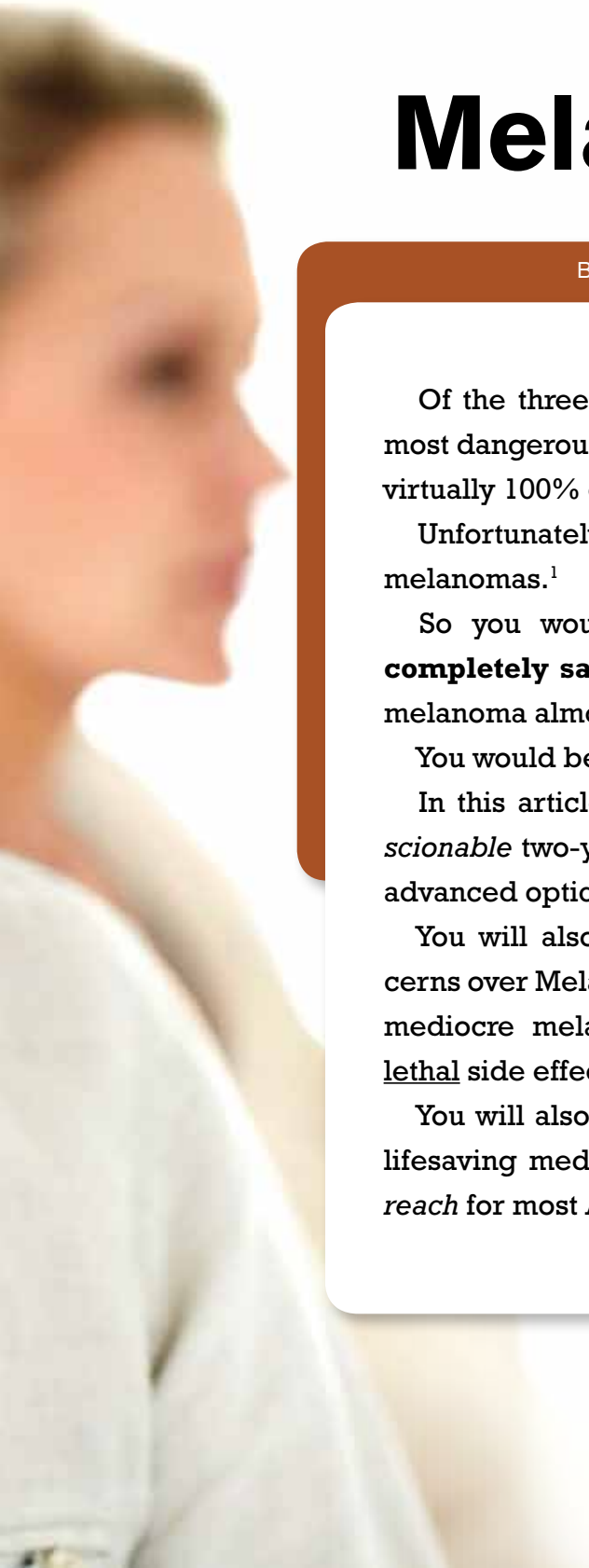


Outrageous FDA Delay Endangers Melanoma Victims

BY AIMEE DINGWELL

Of the three main types of skin cancer, **melanoma** is by far the most dangerous. One American dies of melanoma every hour, yet it is virtually 100% curable if detected in time.[1]

Unfortunately, dermatologists may be missing up to **30%** of curable melanomas.[1]

So you would think that when the FDA is presented with a **completely safe**, ***non-invasive*** device that can help diagnose early melanoma almost instantly, it would receive swift approval.

You would be wrong.

In this article, you will learn of the agency's ongoing and *unconscionable* two-year delay in approving **MelaFind®**, a technologically advanced optical device that boasts a **98%** melanoma detection rate.

You will also discover how even as the FDA cited baseless concerns over MelaFind®'s "safety", they *fast-tracked* approval for a costly, mediocre melanoma drug costing **$30,000** ***per dose*** with potentially lethal side effects.

You will also find out how FDA bureaucracy and bias are sending lifesaving medical innovations like MelaFind® overseas—and *out of reach* for most Americans. >>

Melanoma Detection: Methods, Flaws, and Advances

Unlike other cancers that start inside the body, melanoma begins on the skin's surface and is typically curable if caught early. But early detection is often dependent on a doctor's ability to make educated decisions on which moles they feel are necessary to biopsy.

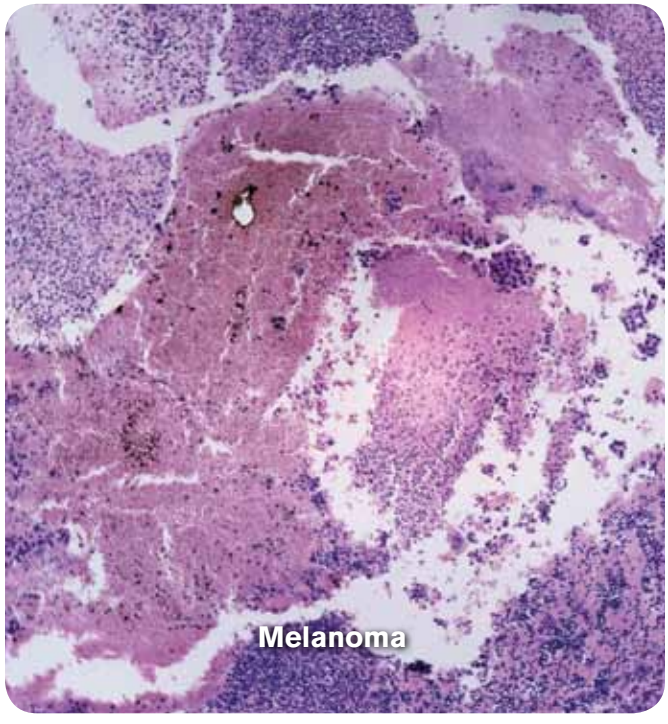
Dermatologists consider whether or not to biopsy the hardest decision they have to make on an hourly basis.

The reason?

The average middle-aged Caucasian has **50** to **60** variously colored moles, or lesions, all over the surface of his or her body. While there may be some that squarely fit the profile of a melanoma, frequently patients present with five, ten, or *more* suspicious moles.

To biopsy every suspicious lesion is cost-prohibitive and leaves the patient with multiple incisions and scars for life. Yet the only way to know for sure if a suspicious skin lesion is or is not an early-stage melanoma is to do a biopsy. Dermatologists are thus confronted with critical decisions as to which lesions to biopsy.

In that decision, according to Dr. Joseph V. Gulfo, CEO of the company that developed MelaFind®, dermatologists today are missing at least **30%** of curable melanomas. They also have to biopsy **50** benign lesions for every melanoma they do find. "Think about that. The value of a false positive is a minimal concern compared to missing a melanoma. Yet doctors are still missing cancerous lesions. They don't want to miss, but they are."


Melanoma

Contrast this with **MelaFind®**, a multi-spectral camera combined with sophisticated algorithms and software to image each potentially cancerous lesion. The image is then compared against a database of more than **10,000** biopsied lesions and 600 confirmed melanomas to provide the dermatologist with an immediate reading.

Each lesion is categorized as: 1) unreadable; 2) positive (biopsy); or 3) negative. According to Gulfo, study results show that the device's positive reading is associated with a detection rate of more than **98%**, while the negative result is associated with a biopsy ratio of **7.6:1**. This means that with MelaFind® dermatologists only have to biopsy **7.6** suspicious lesions to diagnose **one** melanoma. "Right now you have doctors at a **70%** detection rate and up to a **50:1** biopsy rate," says Gulfo. "The number of lives saved would be impressive."

Without advanced technological devices like **MelaFind®**, dermatologists will continue to decide which moles should be biopsied—with the same rate of human error. This means they will have to do about 50 expensive, mutilating and time-consuming biopsies for every one melanoma diagnosed. In terms of health care cost efficiency alone, MelaFind® represents a much-needed productivity advance.

For this reason, researchers consider MelaFind® to be a lifesaving innovation, one the medical community welcomes. "I can speak for my colleagues," said Dr. Darrell Rigel, a professor of clinical dermatology at New York University. "The first response when hearing about MelaFind® is 'When is it going to be available?'"

Bureaucratic Inefficiency Blocks Innovation

While **MelaFind®** is safe and non-invasive, it is the first of its kind. The device is an enormous advance.

Knowing this could prompt extra interest by regulatory officials, Gulfo, who is a veteran of drug development, decided to be more aggressive than most device applications. He spent a year upfront with the FDA, meeting with the agency three times to determine the best study design and define parameters for safety and effectiveness.

The product's application received expedited review status by the FDA's Center for Devices and Radiologic Health and the company successfully entered into a binding protocol agreement, of which only about 10-12 have ever been agreed to by the FDA, noted Gulfo.

The company then conducted the largest study ever done for melanoma diagnosis. "We approached this with the discipline, the rigor, the stringency of a drug and biologic," he said. "The approval pathway is very similar to a cancer drug or biologic cancer trial. You need one pivotal trial. And that's what we did," he said.

Gulfo submitted the product for approval in **June 2009**, limiting its use to dermatologists. The FDA later asked Gulfo to expand the scope of the device to general physicians as well. In November 2010, an FDA panel voted **8-7** (with one abstention) to approve the diagnostic, with members objecting on grounds of safety, stating that the risk of a misdiagnosis from an "unequivocal finding" outweighed the benefit of the significant improvement in early detection. Overlooked by the FDA are the suspicious lesions that are not biopsied because of a judgment error on the part of a dermatologist.

Under the FDA's review process Advisory Panel Committee votes are used as recommendations for approval to the Commissioner.

Positive panel votes do not guarantee approval—and approval has yet to be granted by the FDA.

Citizens Petition for Lifesaving Technology

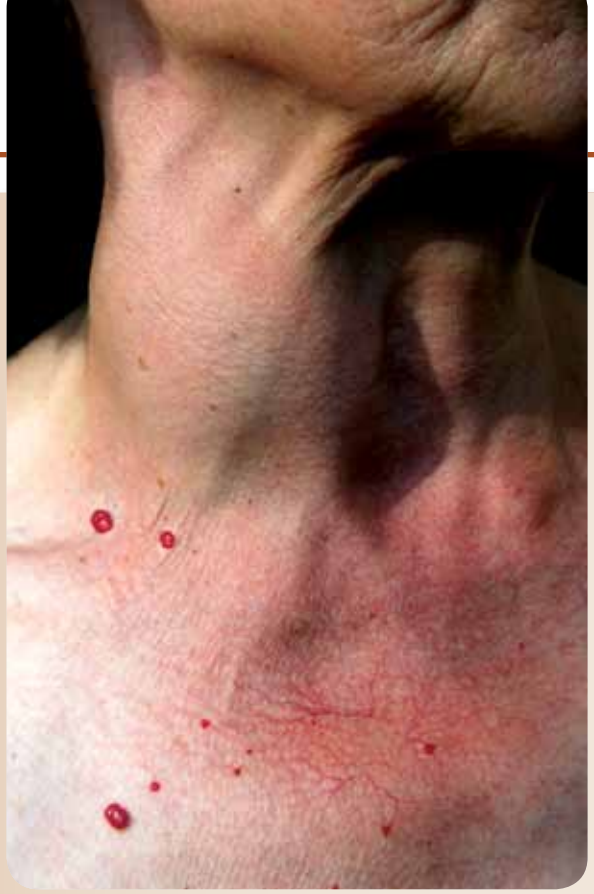
The company has since filed two amendments to the application to address the FDA's concerns with the device, including now limiting its scope to dermatologists and creating a training program, but has had no FDA response despite repeated requests for a meeting.

This silence prompted the company to file a first-ever Citizens Petition in May 2011, which legally demands current FDA Commissioner Dr. Margaret Hamburg to provide a response within 180 days. "We're inviting the commissioner to shine as big a light as possible on the review, because we want transparency," said Gulfo. "We have done everything we can to make the benefit-risk evaluation as emphatically positive as possible for the product and stop one American an hour dying from melanomas being missed. Now it is up to the FDA."

Despite all this, the **MelaFind**® device is ***still*** under review, some two years after submission to the FDA's Center for Devices and Radiological Health.

Ultimately the FDA claims its reasoning for withholding approval is *safety*.

The agency wants an additional trial to be conducted despite having previously outlined approval requirements as part of the initial protocol agreement. Certain members of the committee were concerned that a non-dermatologist would misinterpret



Melanoma

- One American dies of melanoma every hour, yet it is 100% curable if detected in time.
- Owing to flawed methodology, dermatologists may be missing up to **30%** of curable melanomas.
- An application was filed in June 2009 for **MelaFind**®, a completely safe, non-invasive device that can help diagnose early melanoma with **98%** accuracy.
- Citing concerns over "safety," the FDA is still reviewing the application for this lifesaving technology, while fast-tracking approval for ipilimumab (Yervoy™), a $30,000-per-dose, largely ineffective melanoma drug with potentially lethal side effects, including **enterocolitis**, **hepatitis**, **dermatitis**, and **neuropathy**.
- MelaFind® was readily approved by the European Union in September 2011, while the technology languishes here in the US thanks to the FDA.
- Reports show that FDA bureaucracy and bias are sending other lifesaving innovations like MelaFind® overseas and out of reach for most Americans.

the device's unreadable findings as an absence of disease, an assertion that Gulfo and other dermatologists find to be out of touch with how real-world medicine works and infuriating given the device was originally intended to be used only by dermatologists.

"Their concern was that a non-dermatologist would not know what to do with unequivocal results," said Gulfo. "I do not agree with that at all. That would be like an OB/GYN saying that because a mammogram is unreadable, there is nothing to worry about. The correct response for an OB/GYN is to state 'I am sorry. I need you to come back for another mammogram or even better, obtain a far more accurate MRI of the breasts that does not emit cancer-causing radiation."

Dangerous $30,000-Per-Dose-Drug Approved in Record Time

Meanwhile, in March 2011, the FDA's Center for Biologics Evaluation and Research approved a drug called Yervoy™ (ipilimumab) to treat advanced melanoma, based on data that the drug extended survival by about ***four months***.

Yet it has potentially life-threatening side effects that are so severe that the FDA required manufacturer Bristol-Myers Squibb to place a boxed warning on its prescribing information and documentation.

The side effects relate to immune-mediated adverse reactions due to T-cell activation and proliferation, including **enterocolitis**, **hepatitis**, **dermatitis**, **neuropathy**, and **endocrinopathy**.

Still, Yervoy™ was approved in record time under priority review in just seven months. "I'm a huge fan of anything that can help patients," said Gulfo. "But the data are that, while there were some great responders, overall ipilimumab (Yervoy™) added just four months of life. Four months of the least productive, lowest quality, and most expensive life." Yervoy™ costs about **$120,000** for four doses. That equates to **$30,000** dollars a month of life riddled with horrific side effects, though use of Yervoy™ in earlier-stage melanoma patients might eventually prove to be more cost effective

"Detect melanoma at the earliest, most curable stage," noted Gulfo, "and you'll have forty years of high quality life! One of the massive ironies here is there is a tremendous disconnect between the FDA's laudable goals and what is happening as they stymie innovation that could save lives," Gulfo said. "It's almost as if the FDA didn't get the memo."

Bureaucratic Resistance Exports Innovation Overseas

Gulfo blames the delay on what he calls "innovation inertia," fostered in part by the FDA's long history of turnover and unstable leadership. In the last nine years, the beleaguered agency has had four commissioners, dotted by excessive periods of no leadership in between posts. "Yes, continuity is a big problem at the FDA," said Gulfo, "and it is worse on the device side." In February, FDA's Center for Devices and Radiologic

Europeans Benefit As Americans Die

In September 2011, **MelaFind**® was approved for use by dermatologists throughout the European Union, with initial introduction into the German healthcare system.

Incidence of melanoma has *doubled* in Germany over the past 10 years, where melanoma mortality rates are the highest in Europe. Approximately 20,000 Germans will be diagnosed with melanoma by 2016.[2]

Compare that to the US, where melanoma rates have risen steadily over the past 30 years, with an expected **70,230**[3] new cases in 2011 alone.

Thanks to the European Union's enlightened approval process, driven by hard science and public interest rather than profiteering and industry bias, Germans will now benefit from a technology that may *eliminate* skin cancer deaths.

American melanoma victims in the meantime run a higher risk of missed diagnoses and death as the **98% accurate** MelaFind® technology languishes in the limbo of the FDA's irrational and *irresponsible* approval process.

Health (CDRH) Director Dr. Jeffrey Shuren testified before the Subcommittee on Health of the Committee on Energy and Commerce that high rates of turnover were affecting the center's ability to efficiently approve product applications.[4] The result is stymied innovation and unnecessary delays in the availability of life-saving products for the public.

Just weeks before, FDA and CRDH launched the "Innovation Pathway" program, "a priority review program for new, breakthrough medical devices designed to encourage cutting-edge technologies among medical device manufacturers," according to an FDA press release.[5] The program is meant to "accelerate the development and regulatory evaluation of innovative medical devices."

"So here you have another irony," said Gulfo. "We have just what the innovative program is stated to be looking for and it is right in front of them."

While the FDA appears to want to fuel innovation, the reality is that it is more comfortable approving a toxic, late-stage cancer drug—a familiar model in drug development—than approving a safe, non-invasive diagnostic device because it is novel. "Yervoy™ is a pretty common story in cancer drug approval," said Gulfo. "Drug developed for late-stage disease shows some reasonable benefit. In fact, that is every story in cancer drug approval. But we are a breakthrough."

It is this apparent aversion to progress and bureaucratic nitpicking that is causing patient groups, industry groups, and investment groups to sound the alarms that FDA's policies and procedures are burdensome, unclear, and threatening medical innovation itself. "Venture capitalists are openly saying they won't invest in companies if trials are done in the United States because they don't want their returns to be based on an FDA decision," said Gulfo. "So innovation is leaving America. Not even the big companies are doing their innovative work here."

Earlier this year, a report by investment house PriceWaterhouseCoopers showed that medical technology innovation, long centered in the United States, is moving offshore and that US consumers could eventually be the last to have access to innovative medical technology.[6]

A second survey of more than 350 medical device development experts sponsored by the Institute for Health Technology Studies at Northwestern University found that two-thirds of small medical device and diagnostic firms look to Europe for their first regulatory clearances.[7]

Not surprisingly, **MelaFind**® has already been approved for use in the European Union. (See Sidebar.)

"We are a test case. Everybody is watching this. We hit every endpoint and we hit every part of the innovation program. If FDA doesn't approve this—we say innovation is leaving, investment is drying up—it's all gone," said Gulfo. "If this doesn't get approved, it's the death knell. This case is much bigger than just **MelaFind**®. I believe a whole industry is at stake."

Summary

One American dies of melanoma every hour, yet it is virtually 100% curable if detected in time. Owing to flawed methodology, dermatologists may be missing up to 30% of curable melanomas.

An application was filed in June 2009 for **MelaFind®**, a completely safe, advanced optical diagnostic device that can help diagnose early melanoma with **98%** accuracy. Citing concerns over "safety," the FDA is still reviewing the application for this lifesaving technology, while *fast-tracking* approval for ipilimumab (Yervoy™), a $30,000-per-dose, largely ineffective melanoma drug with potentially lethal side effects.

MelaFind® was approved by the European Union in September 2011, while the technology languishes here in the US thanks to the FDA. Numerous reports show that FDA bureaucracy and bias are sending other life-saving medical innovations like MelaFind® overseas and out of reach for most Americans. ●

If you have any questions on the scientific content of this article, please call a **Life Extension®** Health Advisor at 1-866-864-3027.

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BREAKING NEWS AS WE GO TO PRESS

FDA Succumbs to Pressure, MelaFind® Now "Approvable"

The FDA's seven-year war against common sense and logic in the case of MELA Sciences Inc.'s MelaFind® device may be finally coming to an end. After nearly a decade of ignorance and obstruction, the FDA is reversing an earlier decision that flatly rejected the MelaFind® device, costing untold lives in the process. In a *Wall Street Journal* article that appeared on September 27th, 2011, written by Thomas M. Burton, it was revealed that the FDA sent a letter to MELA Sciences Inc. stating its intention to review the device for approval. Inherent in this reversal is the acknowledgement by Dr. Jeffrey Shuren, the FDA's top regulator, that his staff "made the wrong call" when they decided to reject the device before ever holding a meeting of its advisors to discuss it.[10]

The government ineptitude on display should come as no shock to readers of this magazine. The original decision carried with it lethal consequences for sufferers of cancerous lesions that may have been detected earlier with the advanced technology offered by MelaFind®. Thankfully, the company filed a citizen's petition that forced the FDA to review the case and acknowledge its error. As we wait for the government to move at its normal excruciatingly slow pace to get this device in the hands of dermatologists, MelaFind® has already won approval for marketing in 27 European nations.

What is Melanoma?

Melanoma is the deadliest form of skin cancer, and if not caught early, it is one of the deadliest of *all* cancers, as there is no effective treatment for late-stage disease.

What's more troubling is melanoma is on the rise. Over the last 25 years, the incidence of melanoma in the US has nearly quadrupled, according to the National Cancer Institute. Last year, **68,130** Americans were diagnosed with melanoma, and **8,700** lost their lives to this deadly skin cancer. Its main risk factors? Sun exposure and family history.[8]

So what is melanoma? We all have freckles and moles. Melanomas are atypical moles. Excessive sun exposure can cause the uncontrolled growth of skin pigment cells called melanocytes, leading to lesions that may look like harmless, slightly irregular moles, when, in fact, a serious cancer is growing just under the skin. And while melanomas typically appear on the shoulders, legs and hips, they can show up anywhere on the body, including the scalp, between the toes, and rarely, internally.

The hallmark characteristics of a melanoma mole have been labeled the **ABCDEs** of melanoma:[9]

A – **Asymmetry** (one half of the mole is different than the other half)
B – **Border irregularity** (mole has uneven, fuzzy, notched or scalloped edges)
C – **Color changes** or multiple colors (usually blue, black, or dark brown)
D – **Diameter** greater than 6 mm (larger than the width of a pencil eraser)
E – **Evolving** (a change in ABC or D within weeks or months)

If caught early, however, melanoma is almost **100%** curable. But the line between life and death is very thin, literally. According to Dr. Darrell Rigel, a professor of clinical dermatology at New York University's Langone Medical Center, the most important prognostic factor for survival in melanoma is the thickness of the mole, or how far down the melanoma has penetrated into the skin.

Most people will survive having a melanoma if it is removed when it is 1/32nd of an inch, or .75 mm deep. However, less than **50%** of people will survive a melanoma that is 1/8th of an inch deep.

You are at an increased risk for melanoma if you have fair skin, many irregular moles, a personal or family history of melanoma or other skin cancers, or a history of excessive sun exposure, severe sunburns, or frequent use of tanning beds. *However, studies have shown that about **50%** of people who develop melanoma have no risk factors.*

For these reasons, taking preventive measures, like wearing SPF clothing and adequate sunscreen whenever you plan to be in the sun, eating right, exercising, and being vigilant about early detection, are essential to defending against melanoma and saving your life.