KerrisdaleCapital

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Pulse Biosciences, Inc. (PLSE)

High-Voltage Hype Set to Short-Circuit

We are short shares of Pulse Biosciences, a ~$400mm medical-device company with 13 employees, zero revenue, and one focus: developing and commercializing a technology it calls "Nano-Pulse Stimulation" (NPS), in which cells are exposed to very strong electrical fields for very brief periods of time in hopes of killing them. Pulse claims that this method of killing cells constitutes a "novel therapeutic tissue treatment platform" with the potential not only to destroy tumors directly but also, in the words of the company's chief scientific officer, to "essentially transform[them] into vaccines to direct the immune system to destroy them." On the basis of this high concept (as opposed to any significant commercial or technical progress), Pulse's stock price has increased six-fold since its May 2016 IPO.

This run-up is senseless. Contrary to Pulse's highly selective narrative, even if NPS one day performed as advertised, it would still have little value. For one thing, an existing ablation device called the NanoKnife, which has been on the market for a decade, *also* kills cells by exposing them to very strong electrical fields for very brief periods of time. While Pulse insists that its technology, by using somewhat stronger fields for somewhat briefer periods, generates wildly different effects, the scientific literature argues otherwise: many allegedly unique benefits of NPS, like the induction of apoptosis (a form of programmed cell "suicide") and the stimulation of the immune system, apply not just to NanoKnife but to a wide range of other run-of-the-mill treatments. From a clinical perspective, Pulse's NPS is nothing special, especially relative to NanoKnife – which, in turn, is a perennial flop with less than $20 million in annual revenue.

Worse still, our review of published NPS results reveals that the technology *doesn't* perform as advertised. To the contrary, it's often appallingly ineffective. For instance, in the only formal NPS clinical trial published to date, Pulse researchers treated three patients with skin cancer and – in an outcome far worse than standard surgery – left two with residual cancer and a third with discolored and anomalous-looking (but supposedly, for the time being, benign) lesions. Very recently, new research *funded by Pulse itself* concluded that "even after the most intense treatments" a sizable fraction of human cancer cells across a range of cancer types simply *cannot be killed* by NPS – an alarming phenomenon whose cause remains a complete mystery. The unexpected discovery of this "residual resistivity" or "tolerance" – published online in December, headed for print in May, yet, to our knowledge, never mentioned by Pulse management – may by itself wipe out what little commercial value NPS might have had. What's the point of a method for killing cancer that can't kill cancer?

Pulse's technology has barely made it off the drawing board, yet it's already proven itself to be weak, unreliable, and undifferentiated. Investors with high expectations are in for a shock.

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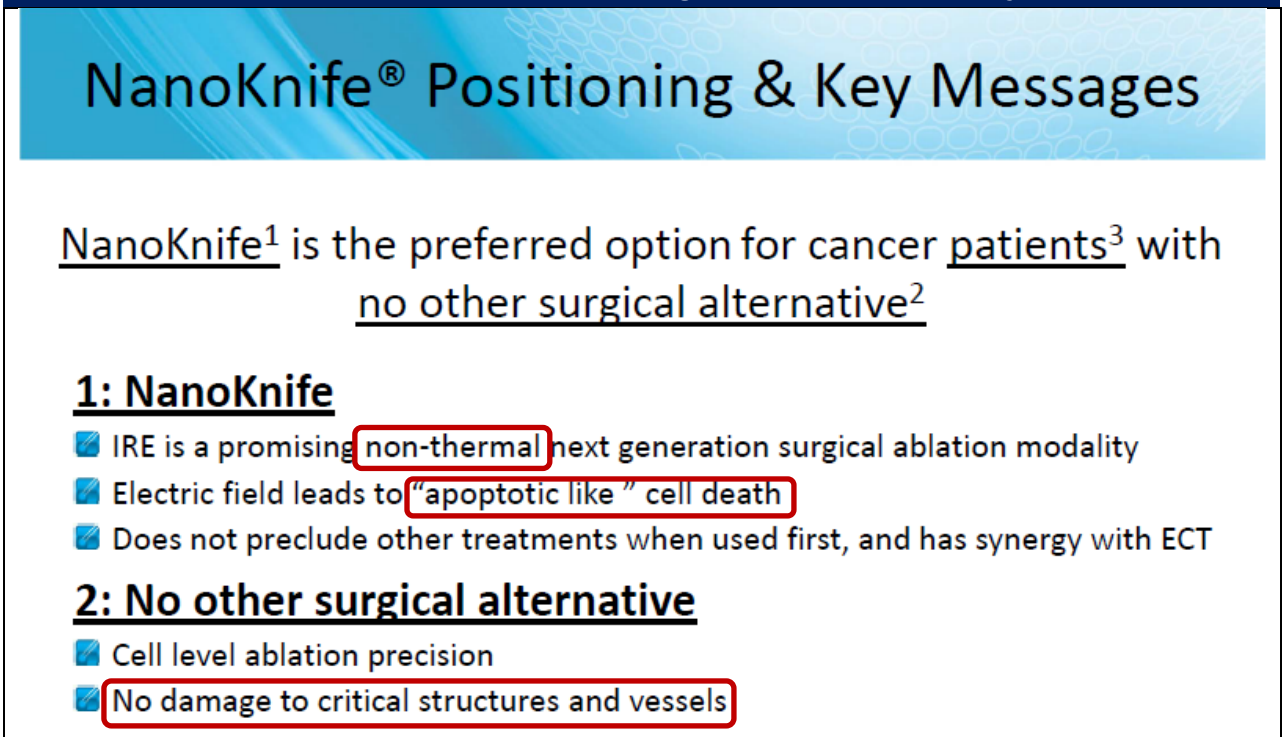
I. Investment Highlights

Pulse's NPS technology is far less special than it claims. Pulse contends that "NPS will provide unique benefits to patients in a wide variety of medical applications,"[1] asserting that, while other ablation modalities using extreme heat or cold to destroy tumors "generally lead[] to cellular necrosis" (uncontrolled cell death driven by physical injury), NPS "offers a **non-thermal** and non-ionizing ablative technology that can be selectively tuned to **induce apoptosis**," or programmed cell death. "[T]his less destructive approach," according to Pulse, "lends itself to a number of applications including tumors which would otherwise be inoperable because of **proximity to critical structures**" (emphasis added).[2]

However, irreversible electroporation (IRE) – a technology very similar to NPS and already commercialized for years under the brand name NanoKnife – has been pitched in almost exactly the same way, as this selection from a 2012 marketing presentation demonstrates:

Selection from NanoKnife Marketing Presentation, February 2012



Source: AngioDynamics. Red highlights added by Kerrisdale.

Furthermore, while Pulse uses limited evidence from animal models to suggest that NPS can prevent cancer recurrence, irreversible electroporation produced similar results four years ago, when a team of researchers found that, after using IRE to destroy tumors in mice and then

[1] Pulse 2016 10-K, p. 3.
[2] Pulse 2016 prospectus, p. 27.

injecting the mice with a second batch of cancer cells, "growth of the second tumors was…significantly reduced or prevented entirely" (1). Indeed, more broadly, what Pulse claims to be NPS's most important benefit – its purported ability to cause cell death in a way that stimulates the immune system – is shared by a wide range of therapies, including cryoablation, photodynamic therapy, radiation therapy, focused ultrasound ablation, radiofrequency ablation, and more. If NPS can't "provide unique benefits" like Pulse says, then it makes no sense for such an early-stage technology – years away from generating meaningful revenue, and supported by published data from only four human patients – to command such a high valuation.

Similar technologies have repeatedly fallen short of expectations. While Pulse's marketing message closely resembles that of NanoKnife (manufactured by AngioDynamics, which acquired the technology in 2008 for just $25 million[3]), that should come as no comfort to Pulse shareholders, since NanoKnife has proven to be a serial disappointment both clinically and commercially. For instance, in a surprising failure, a clinical trial testing the use of NanoKnife in lung cancer ended early when it became clear that the treatment failed to eradicate many tumors (2) – notwithstanding preclinical evidence, like Pulse's, of positive immune effects. A decade after launching, NanoKnife still produces less than $20 million of annual revenue – a small part of a relatively small yet crowded market for nonsurgical tumor ablation.

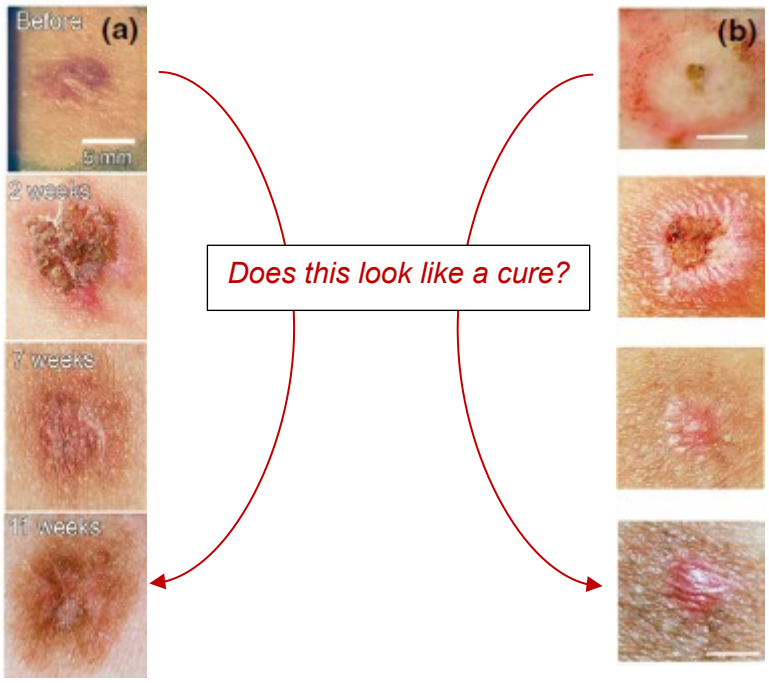
Similarly, while some animal models have suggested that radiofrequency ablation stimulates significant immune benefits, a randomized controlled trial in *humans* with liver cancer proved that the therapy delivered results that were significantly *worse* than those of conventional surgical resection (3). Another technology, high-intensity focused ultrasound (HIFU), has likewise shown signs of enhancing immune responses to cancer, yet its results in humans were so weak that it struggled to achieve FDA approval, and the technology's leading manufacturer, a French company called EDAP, earns almost zero profit from it. In general, tantalizing hints that new ablation modalities might confer meaningful anti-cancer immunity have failed to translate into real-world success, an outcome that we fully expect to repeat for Pulse. There's no room in the marketplace for a NanoKnife "me too" when the original NanoKnife has failed to gain much traction. Even if Pulse's technology did what it was supposed to do, it would have no realistic value proposition.

Pulse's data indicate that NPS is impotent and unreliable. In the only formal study of NPS in humans yet completed and published, Pulse researchers treated ten small tumors caused by basal-cell carcinoma (a type of skin cancer) across three patients. While Pulse has spun this study as an early win, three out of the ten tumors remained cancerous 15 weeks after treatment; by contrast, the most effective treatment for this cancer, a technique called Mohs surgery, almost always succeeds, with recurrence very rare even five years later. Not only did NPS fail to eliminate 30% of the tumors; it failed on two out of three patients. The third, while judged cancer-free on the basis of histological data, was likely unhappy with the "improvement" of her

[3] See AngioDynamics FY 2009 10-K, p. 4.

two lesions, which in our view look even more troubling *after* treatment (last row of photos) than before treatment (first row of photos):

Pulse's Results in One Patient's Basal-Cell Carcinoma



Source: Nuccitelli et al. 2014 (4)*, Kerrisdale analysis*
Images depict two different tumors on a single patient before treatment and two, seven, and eleven weeks after treatment, from top to bottom.

For one of the other two patients, not only did NPS fail to rid him of cancer; it also appeared to give rise to two instances of seborrheic keratosis, a benign skin growth that *looks* like skin cancer – an unpleasant result not just for the patient but for Pulse, which hopes to one day treat this condition[4] yet may somehow cause it.

These startlingly bad results are consistent with a longer track record of weak and inconsistent NPS data. The latest and perhaps the most worrisome example is a study *paid for by Pulse itself* that shows for the first time that, across a variety of healthy and cancerous human cell lines, sizable (10%+) fractions of cell populations exposed to NPS boast "an unusual level of…tolerance" and simply don't die, no matter how many times they're zapped (5). Disturbingly, while the authors of the study tried to take the sting out of this discovery by blaming it on some artifact of the experimental methodology, they concluded that the phenomenon of NPS resistance or tolerance is quite real – yet its cause remains a mystery.

[4] See e.g. Pulse 2016 10-K, p. 6.

When NPS failed to completely kill tumors or prevent their recurrence in previous studies, as it often did, researchers could always fall back on the excuse that they just hadn't used enough pulses. The new study, however, exposes that excuse as hollow and underscores just how poorly the effects of NPS are still understood. Since cancer is, by definition, a disease of aberrant growth, and other existing ablation modalities can in fact reliably kill cells, a treatment like Pulse's NPS that unaccountably only kills some parts of tumors some of the time is worthless.

If Pulse's technology were as good as it claimed to be, it would still falter in a market already full of technologies with similar stories. But with so much evidence quickly stacking up against NPS, we believe it's dead on arrival.

II. Company Overview

Pulse Biosciences: Capitalization and Financial Results

Capitalization	
Share price ($)	$23.07
Fully diluted shares (mm):*	
Shares outstanding	14.1
Dilutive impact of warrants/options	1.7
Total	15.9
Fully diluted market cap ($mm)	$ 366

Financial results ($ mm)	2015	2016	2017†
Revenue	$ -	$ -	$ -
Oper. cash flow	(3)	(8)	(14)
Cash	4	16	8

**Pro forma for Pulse's February 2017 equity issuance (at a price of $6.10 per share).*
†2017 values represent Kerrisdale projections. Pulse management indicated on the company's May 4, 2017, earnings call that cash use in 2017 would be $13.5 million.
Source: company filings, Kerrisdale analysis

Though technically founded in May 2014, Pulse Biosciences grew out of an entity formed in 2000 (initially called RPN Enterprises and later renamed BioElectroMed) created by Richard Nuccitelli, a former UC Davis professor and now chief scientific officer of Pulse who retired from academia to pursue his fortune. In the early 2000s, Nuccitelli grew excited about early animal studies showing that strong but brief electrical pulses (on the order of 100 nanoseconds in duration) could eliminate tumors. While research findings in this area, many of them co-authored by Nuccitelli and funded by government grants, trickled in over the years, the field remained obscure, with only a handful of groups involved and no apparent outside commercial interest. By 2008, Nuccitelli's BioElectroMed entity seemed to be more focused on an unrelated technology called the Dermacorder, designed to assess wound healing and even diagnose cancer by measuring electric fields; an old version of BioElectroMed's web site boasts that the device was "featured on Star Trek Tech [on the] History Channel."

But the Dermacorder apparently amounted to little, and by 2013 BioElectroMed returned its focus to what it then called "Nanosecond Pulse Ablation." A "Partnering" page on its site noted, "We seek corporate partners…To inquire about partnering opportunities, please contact us." But no partners emerged. Ultimately the small investment bank MDB Capital – a firm with a checkered past that includes packaging and taking public many companies that proved disastrous for long-term shareholders – helped BioElectroMed roll up a number of patents related to nanosecond pulsed electric fields, some of which were previously held by a handful of universities, including Old Dominion and Eastern Virginia Medical School. A November 2014 private placement infused the new roll-up entity with $8 million in cash and valued it at $20 million in total, or $2.67 per share (88% lower than the current price). Finally, what was now called Pulse went public in May 2016 at a price of $4 per share.

Little happened in Pulse's first several months as a public company, and its stock price ranged between $4 and $6. On February 10, however, Pulse issued a press release announcing that Robert Duggan, a serial entrepreneur who became a billionaire after selling the drug company

Pharmacyclics to AbbVie, and Maky Zanganeh, a former dentist and Duggan's COO at Pharmacyclics, bought significant stakes in the company, including purchasing $5 million of newly issued shares directly from the company at a price of $6.10. Investors, acting as if this shift in ownership somehow altered the value of Pulse's underlying technology, drove the stock dramatically higher from there. Indeed, the price has become so frothy that Pulse recently announced that MDB Capital had waived lock-up provisions a month early for pre-IPO holders of 28% of the company's shares; apparently these holders were so eager to sell at current prices that they didn't want to risk waiting even one more month, despite the ugly optics.

While the past successes of Pulse's new minority shareholders deserve respect, they can't change what the technology is or how well it works. To be sure, NPS is still very early in its development, having been used on only a handful of human patients to date, but, with no meaningful edge over alternative ablation modalities and an accumulating body of evidence highlighting its weakness and inconsistency, Pulse cannot, in our view, justify anything close to its current valuation – no matter who owns its shares.

III. Pulse's Technology Is Nothing Special

Out of context, Pulse's story sounds good. The first page of the company's IPO prospectus sets out the official line:

> For the treatment of cancer, we believe that we can trigger a signaling cascade within the tumor cells that ends in immunogenic apoptosis. Immunogenic apoptosis is a process in which cells are induced to die in a natural way, initiating their own programmed cell death, engaging the immune system to clear damaged, diseased, or aged cells and enrolling cytotoxic T cells to recognize and eliminate cells of the same tumor type. We believe we are the only medical device company with the intellectual property, technology, and know-how to be able to produce this natural cell death using NPES[5] to initiate cell signaling that induces the targeted adaptive immune response.[6]

Not only can Pulse's device kill cells, the story goes; it can also kill them in a unique way that recruits the patient's own immune system to join the fight.

But is Pulse truly "the only medical device company" with these abilities? Pulse is at pains to distinguish its "nanosecond" pulses (which, in clinical applications, have actually been ~100-nanosecond pulses) using electric field strengths of tens of thousands of volts per centimeter from the characteristics of another technology, irreversible electroporation (IRE), which uses pulses ~100x longer at electric field strengths ~10x weaker. According to Pulse, irreversible

[5] By the time of its 2016 Q3 10-Q, Pulse began to refer to its technology as "Nano-Pulse Stimulation" However, previously it used the term "Nano-Pulse Electro-Signaling" (NPES), while academic papers generally say "nanosecond pulsed electric field" (nsPEF). These terms are all synonymous.
[6] Pulse 2016 prospectus, p. 1.

electroporation – marketed by the publicly traded medical-device company AngioDynamics under the name NanoKnife – "cause[s] cell membranes to irreversibly permeabilize, resulting in necrosis (death) of the tumor cells," while Pulse's technology, by contrast, "transiently permeabilizes internal organelles which can lead to a signaling cascade ending in immunogenic apoptosis rather than necrosis."[7]

The scientific literature, however, paints a different picture: irreversible electroporation is generally regarded as causing apoptosis. Consider the following passage from a study of IRE in human prostate cancer (emphasis added) (6):

> Unlike other [focal therapy] modalities, [IRE] relies on a non-thermal mechanism to induce cell death. IRE uses needle electrodes placed in or around a targeted volume of tissue to deliver a series of brief direct-current electrical pulses with the intention of inducing a permanently porous cell membrane. This disrupts cellular homoeostasis **resulting in apoptosis**.

This summary is not meant to be controversial; rather, it merely states the consensus. Another recent IRE study used similar language (7):

> Unlike RFA [radiofrequency ablation] and MWA [microwave ablation], **IRE induces apoptotic cell death** in the (relative) absence of thermal damage. … IRE thus offers the advantage of preserving underlying structural integrity and architecture due to **the absence of necrotic cell death**…

Moreover, while Pulse harps on NPS's ability to induce apoptosis, this emphasis is overblown. What exactly NPS does to cells remains murky. As one 2014 paper explained (emphasis added) (8):

> With the complexity of the cellular response to nsPEF [nanosecond pulsed electric fields], the mechanisms and specific pathways leading to cell death have only been partially understood. The early studies focused on the apoptotic response and only recently **early necrosis** was reported by several groups as a separate or **even a predominant mode of nsPEF-induced cell death**.

In short, AngioDynamics' NanoKnife IRE technology causes apoptosis, not just necrosis, while Pulse's NPS technology causes necrosis, not just apoptosis. To depict itself as unique, Pulse has no choice but to gloss over the deep similarities between IRE and NPS, but these efforts are misleading. However interesting the different effects engendered by variations in pulse duration and field strength may be from a scientific perspective, their practical impact on cancer cells appears to be small.

[7] Pulse 2016 prospectus, p. 38.

Indeed, more broadly, there is nothing unusual about non-surgical ablation modalities or other cancer treatments causing cell death by apoptosis. As one 2016 review put it, “Induction of apoptotic programmed cell death is one of the underlying principles of **most** current cancer therapies,” including radiation and chemotherapy (emphasis added) (9). While cells directly exposed to intense heat may die in an uncontrolled, necrotic manner, that’s not the whole story. In the words of another recent review (emphasis added) (10):

> Heat-ablated lesions can be thought of as having three zones: the central zone, which is immediately beyond the application tip and which undergoes ablation-induced coagulative necrosis; a peripheral or transitional zone of sublethal hyperthermia, which mostly occurs from thermal conduction of the central area that is either **undergoing apoptosis** or recovering from reversible injury; and the surrounding tissue that is unaffected by ablation.

As the same review also points out, a similar pattern results from cryoablation, which kills cells via intense cold:

> Direct cold-induced coagulative necrosis occurs at the centre of cryoablative lesions, whereas apoptosis has been observed at their periphery.

Thus, what Pulse cites as a key point of differentiation – NPS’s ability to induce apoptosis – is anything but different. A company with an undistinguished hypothetical product that has barely taken the first steps toward commercialization in a crowded market doesn’t deserve a $400-million valuation.

Many Other Cancer Treatments Stimulate the Immune System

Ironically, Pulse’s rhetorical focus on apoptosis runs counter to its other focus: the potential immunological benefits of NPS. In general, apoptosis is thought to stimulate immune responses far less than necrosis – or even to *suppress* immune responses. A 2009 review of immune responses to cryoablation summarized the traditional view (11):

> Necrosis occurs with mechanical tissue damage, such as cryoablation, and is characterized by cellular breakdown and release of intracellular contents. Many of these intracellular contents can be immunostimulatory. … Apoptosis, or programmed cell death, results in several steps that allow the uptake of cellular debris by both macrophages and dendritic cells, but without causing inflammation and thus stimulat[ing] an immune response. Apoptotic cells do not release their contents…as do necrotic cells. In fact, several studies have shown that apoptosis not only does not stimulate immune recognition, but quite the opposite.

To be fair, over time, further research has demonstrated that in some cases apoptosis *can* give rise to so-called immunogenic cell death (ICD). However, it would be bizarre to suggest that

Pulse's NPS has a monopoly on stimulating the immune system. To the contrary, decades of research show that a wide range of ablation modalities and other treatments can lead to ICD. This is not some special new power that makes Pulse's technology superior to the status quo; it's already widespread.

A recent review by researchers from University College London entitled "Harnessing the Immunomodulatory Effect of Thermal and Non-Thermal Ablative Therapies for Cancer Treatment" gives a sense of how many such therapies appear to enhance immune responses:

Select Ablative Therapies Found to Stimulate the Immune System

Treatment type	Evidence of immune response generation	Evidence on combination therapies
Cryotherapy	Best	Best [68–77]
PDT	Good	Moderate [44, 45]
HiFU	Good	Little
Radiotherapy	Good	Good [78–82]
Electroporation	Limited	Little
LoFU	Limited	Little
Microwave therapy	Limited	Little
Radiofrequency ablation	Good	Moderate [25, 29, 83]

Source: Bastianpillai et al. 2015 (12)*, Table 1*
Note: PDT = photodynamic therapy; HiFU = high-intensity focused ultrasound; LoFU = low-intensity focused ultrasound.

Note that the treatment with the strongest evidence of immune-response generation is cryotherapy, the ablation of tumors using extreme cold; by contrast, electroporation – the treatment most similar to Pulse's NPS – has produced more "limited" evidence. Beyond this list, chemotherapeutic agents including doxorubicin, mitoxantrone, oxaliplatin, and bortezomib, along with the simple physical intervention of applying high hydrostatic pressure *ex vivo,* have also been shown to elicit ICD (13). Pulse's technology is more of the same.

Consider, for instance, radiofrequency ablation – a method of killing cancer cells with intense heat. Japanese researchers showed in 2010 that radiofrequency ablation of a tumor on one side of a mouse's body could significantly reduce the growth rate of an untreated tumor on the other side, "accompanied by massive T-cell infiltration" – evidence of a strengthened immune response sparked by the ablation (14). Another group showed in 2013 that radiofrequency ablation of colorectal cancer in mice "caused a marked increase in intratumoral CD8+ T lymphocyte infiltration," especially T cells specific for tumor antigens. In addition, ablation of a primary tumor retarded the growth of separately induced secondary tumors on other parts of the body, and this effect required the presence of T cells to work (15). In short, radiofrequency ablation doesn't just kill the cancer cells it directly affects; it also triggers the immune system to attack similar cells.

Likewise, consider high-intensity focused ultrasound (HIFU). Mouse studies as far back as 1992 suggested that HIFU led to "stimulation of host tumor immunity" (16). Further studies revealed that vaccinating mice with HIFU-treated tumor cells inhibited growth of subsequently introduced tumors, while T cells extracted from tumor-bearing mice treated with HIFU, when transferred to other such mice not treated with HIFU, could extend survival and even induce tumor regression (17).

Irreversible electroporation also appears to confer a degree of anti-tumor immunity. In 2013, researchers found that, after only partially ablating mouse tumors using IRE, mice with functional immune systems survived much longer than immunodeficient mice – suggesting that, even when IRE didn't eliminate every cancer cell, it still sparked enough of an immune response (in mice capable of it) to enhance health. Furthermore, in tumor-bearing mice treated with IRE and then subsequently re-challenged with the same type of tumors, "growth of the second tumors was shown to be significantly reduced or prevented entirely" – a phenomenon accompanied by "robust" T-cell infiltration in some mice (1). In 2016, another mouse model demonstrated that IRE ablation of the liver could inhibit the growth of a related tumor on the skin, again accompanied by an influx of T cells (18).

Such effects, observed across a wide array of ablation modalities (including NanoKnife's IRE), put Pulse's overblown claims in perspective. The best evidence Pulse has marshaled shows that, in some cases, in certain animal models, NPS treatment can do more than kill the cells it directly affects; it can also stimulate the immune system to target tumors itself. But the same can be said for radiofrequency ablation, cryoablation, high-intensity focused ultrasound, irreversible electroporation, and more. Pulse's findings do nothing to distinguish NPS from the many more established and better understood competitors.

Observed Immune Effects Have Not Translated to Clinical Benefits

Despite intriguing suggestions of positive immunological side effects, however, nonsurgical ablation modalities have often performed poorly in real patients. In the words of one 2017 review (emphasis added) (17):

> [In addition] to lowering the general tumor burden, ablation releases tumor antigens and multiple bioactive molecules such as damage-associated molecular patterns (DAMPs). Combined with general inflammation and immune-regulatory processes of the wound healing response following ablation, this will result in different innate and adaptive immune effects.… **However…responses generally remain weak. Potent antitumor immunity therefore is rarely generated,** as also evidenced by scarce reports of spontaneous regression following ablation.

Irreversible electroporation, for example – the modality most similar to Pulse's NPS – performed surprisingly poorly in a key lung-cancer trial published in 2015, forcing the trial to be cut short prematurely lest more patients receive such ineffective treatment (2). In another recent clinical

trial dubbed the “NanoKnife Electroporation Ablation Trial” (NEAT), researchers were again clearly disappointed by the results, noting that, while NanoKnife treatment appeared to be safe, “[t]he ablation results were less satisfactory, with one-third [of patients] harbouring clinically significant disease following treatment” – a far cry from a consistent cure. Thus, whatever the modest potential immune benefits of IRE, they were not enough to overcome its other limitations, like the difficulty of assessing whether a targeted tumor has been fully ablated in the first place.

These weak results are not unique to IRE; other modalities have produced similar disappointments in the clinic. For instance, in a large randomized trial comparing liver-cancer patients treated with radiofrequency ablation to those treated with conventional surgery, RFA led to substantially worse overall survival and recurrence-free survival, with RFA patients almost 50% more likely than surgery patients to experience a recurrence of their cancer within five years after treatment (3). Again, regardless of whether RFA induced any immune response in these patients, it didn’t matter; overall, they still would have been better off with surgery.

Ultrasound ablation has yielded further disappointments. An unfinished trial using a device called Ablatherm produced by the publicly traded company EDAP found that almost a third of prostate-cancer patients tested positive for prostate cancer within two years of ablation, results so poor that an FDA expert panel voted unanimously in 2014 that there was no reasonable assurance that the treatment was effective. Once more, immunological data generated in animal models failed to translate to a net clinical benefit in real patients.

Indeed, the evidence in favor of nonsurgical ablation is generally weak, as one recent review pointed out (10):

> [C]ommon disadvantages include incomplete ablation, disease recurrence and inferior outcomes…There is a noticeable lack of randomized controlled clinical trials in patients, which is mostly because it is unethical to conduct head-to-head comparisons between ablation and surgical excision when the tumour is resectable.

Over time, the same pattern of disillusionment has repeated again and again: tantalizing hints that killing cells in some novel way will have meaningfully positive knock-on effects, juxtaposed with unimpressive clinical outcomes that relegate the treatment to the small market of patients with no better alternatives. At best, Pulse’s NPS technology will fizzle out in the same way.

Technologies Like Pulse’s Have Been Commercial Flops

With only weak and equivocal clinical data to support them, novel ablation modalities akin to Pulse’s haven’t gained significant market share. The most relevant example is the NanoKnife IRE technology, purchased by AngioDynamics in 2008 for just $25 million (a small fraction of

Pulse's current market cap).[8] The NanoKnife pitch is almost identical to Pulse's, as befits a technology so similar. Both purport to use strong but short electrical pulses, not extreme temperatures, to induce apoptosis; both can point to limited preclinical evidence that this approach triggers an immune response; and both claim they can protect important structures like blood vessels and bile ducts that may be close to targeted tumors. Pulse's NPS, however, remains far from commercialization, while NanoKnife has benefited from a decade of marketing and a large body of clinical research.

After all those years, though, NanoKnife has gained little traction. Across the world, virtually no insurance company or government payor covers NanoKnife ablation,[9] regarding it as "experimental and investigational," not proven or medically necessary.[10] While the FDA has cleared it for the generic indication of soft-tissue ablation, it lacks approval for the treatment of any specific condition; as a result, in the words of a recent sell-side initiation piece, "NanoKnife market adoption has been slow."[11] To our knowledge, the last time AngioDynamics disclosed NanoKnife revenue, in October 2015, it had fallen from an annualized run rate of $17 million[12] to just $12 million, driven by a decline in the sale of new NanoKnife systems (as opposed to disposables used during procedures). While AngioDynamics then stopped providing specific figures, management signaled that NanoKnife market growth continued to be weak:[13]

- January 7, 2016: "[G]aining new capital placements has been a challenge for NanoKnife…As we look to the second half of the [fiscal] year, we have revised our NanoKnife capital outlook to reflect this view until we achieve our reimbursement goals."
- April 7, 2016: "Capital sales of NanoKnife continued to be a challenge this quarter…[T]he revised guidance contemplates near-term NanoKnife capital sales to be below historical run rate levels…"
- January 6, 2017: "The Oncology/Surgery franchise generated revenue [that was]…down 6% year-over-year and was driven by lower sales in a blation products and NanoKnife capital…"

It thus appears that NanoKnife has made little progress beyond the installed base of just 136 units that it had achieved by 2016.[14] If that's all NanoKnife could accomplish in over a decade,

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[8] See AngioDynamics FY 2009 10-K, p. 4. 2008 is when the purchase closed; it was announced earlier, in 2006.

[9] See e.g. Barclays Capital's AngioDynamics initiation report dated February 8, 2017, p. 12 ("A primary challenge for NanoKnife currently is obtaining reimbursement and ANGO believes more studies and clinical data could help that. While it has country approvals and a DRG code in Germany, ANGO continues to seek CMS and NICE (UK) reimbursement for NanoKnife procedures").

[10] See e.g. determinations by Aetna, Priority Health, BCBS of Arizona, BCBS of Florida, and BCBS of Alabama.

[11] Cantor Fitzgerald on AngioDynamics, November 3, 2016, p. 1.

[12] See AngioDynamics August 5, 2015, presentation, slide 21.

[13] Earnings call transcripts obtained via Capital IQ.

[14] See AngioDynamics October 15, 2015, presentation, slide 18.

what hope is there for Pulse – with an extraordinarily similar product backed up by far less research and experience – to build a real business?

While AngioDynamics continues to hold out hope that NanoKnife will flourish one day, it's clear that the market has more sober expectations. NanoKnife accounts for roughly 5% of AngioDynamics' revenue, and the entire firm has an enterprise value of only $636 million, the vast majority of which is obviously attributable to other products. Simply applying AngioDynamics' overall EV-to-sales multiple to an estimate of NanoKnife's sales,[15] we estimate that the market is valuing NanoKnife at just $29 million:

Implied Market Valuation of NanoKnife

(*$mm*)	
AngioDynamics, FY 2016:	
Total net sales	$ 354
NanoKnife net sales	16
AngioDynamics EV	636
EV to net sales	1.8x
Implied NanoKnife value	$ 29
Pulse downside	**(92)%**

Source: company filings, Capital IQ, Kerrisdale analysis

If Pulse somehow merited the same valuation as NanoKnife, its shares would have *92% downside.* Of course, such a valuation is absurdly *generous.* Pulse has 13 employees and no commercial products; it's years from earning significant revenue. NanoKnife, by contrast, is actually in use today. There is simply nothing about Pulse's prototype technology that deserves a 1,200% premium to its closest comparable. If a healthcare provider or payor wasn't swayed by NanoKnife's selling points, then Pulse's pitch will also fall on deaf ears.

Though less similar to Pulse's NPS, EDAP's HIFU product Ablatherm also furnishes an example of a novel ablation tool that has fallen short commercially. While Ablatherm does use heat (generated indirectly by sound waves) to kill cancer cells and thus differs from the purportedly non-thermal approaches of IRE and NPS, it has its own unique selling point: it's *completely* noninvasive, deployed either outside the body or from within a cavity. As discussed above, HIFU has also been found to trigger immune responses. In early 2006, EDAP was a hot stock, quadrupling from ~$5 to ~$20 per share on the back of the company's initiation of clinical trials in the US. But investor enthusiasm was short-lived: Ablatherm's weak results, described above, forced EDAP to abandon its plan to seek approval for the device's use in prostate-cancer treatment and instead pursue a narrower and far less meaningful regulatory clearance to ablate prostate tissue, with no claim made as to treatment efficacy. As a result, Ablatherm, like

[15] Cantor Fitzgerald has estimated that current NanoKnife revenues are $16 million. See initiation piece, November 3, 2016, p. 2.

NanoKnife, still suffers from a lack of insurance coverage. Today EDAP's shares trade at $2.53 – off some 90% from their peak – and the company's HIFU products generated just $1 million of operating income in 2016. Much of the EDAP's small market cap stems not from HIFU but from its kidney-stone-treatment business, which accounted for 61% of its 2016 net sales. Even if we allocate half of the company's enterprise value to HIFU, the valuation is still just $26 million – very close to our estimate of what NanoKnife is worth and, again, a tiny fraction of Pulse's valuation, even though EDAP, for all its flaws, can at least claim to have a finished product to sell.

Approached from any angle, Pulse is massively overvalued *even if NPS technology is all it's cracked up to be.* At best, NPS is a close cousin to NanoKnife, an obscure, poor-selling product frowned up by insurers and unable to gain a commercial foothold beyond a handful of users. The features that Pulse claims distinguish NPS from all other cancer treatments and ablation modalities – its ability to foster apoptosis and spark an immune response – are in fact commonplace yet have done little to drum up sales. Beyond the bluster, Pulse's technology is nothing special.

IV. Pulse's Technology Is Impotent and Unreliable

Even if Pulse's NPS lived up to its billing, it would have little value in a world where NanoKnife and other novel ablation modalities have faltered. However, a detailed review of the available published data shows that NPS is disturbingly inconsistent and ineffective. Thus its overvaluation is even more extreme.

Pulse's Basal-Cell Carcinoma Trial Was a Failure

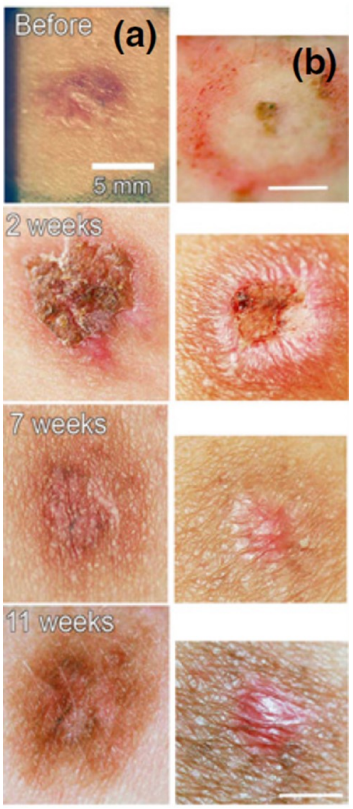
NPS has almost never been used on humans. The first reported case was published in 2007, when a researcher *self-administered* 200 20ns-long electrical pulses at a field strength of 6.5 kV/cm to attempt to ablate a small basal-cell carcinoma (BCC). Within six weeks, the BCC was replaced by a scar, and surgical excision later showed that the cancer was gone (19). But this informal, un-blinded self-study, described in only a few sentences in an old paper, hardly constitutes a formal trial. The first and only such trial to date was published in 2014 in a paper whose lead author is now Pulse's chief scientific officer (4).

Taken at face value, the trial was a success. As Pulse later said, "We believe the study demonstrated NPES is safe and can offer a fast and scarless alternative to current standard of care."[16] Pulse has also highlighted two sets of photos of lesions treated in the trial, cherry-picking the most attractive results and omitting more disturbing images.

[16] See Pulse March 28, 2016, presentation, slide 17.

Notwithstanding Pulse's selective presentation, it's clear that this trial was, in reality, a failure. Pulse only treated three patients, each of whom had multiple BCC lesions – ten in total. Fourteen to fifteen weeks after NPS treatment, based on histological analysis, three of the lesions still harbored cancer; the other seven did not. It's important to note the distribution of these failures: *two out of the three* patients still had at least one cancerous lesion, indicating that, even for a single patient, the effects of NPS are unpredictable and inconsistent. The third patient, though determined by the authors to be cancer-free, continued to have anomalous-looking lesions in the same locations, the likes of which would send anyone to the dermatologist:

Before and After Images of Basal-Cell Carcinomas Treated by NPS in a "Successful" Patient



Source: Nuccitelli et al. 2014 (4)

While the published write-up of this trial claims that NPS "was sufficient to cause most of these lesions to disappear during the ensuing several weeks," "disappear" hardly seems the right word for what happened. Every lesion in every patient developed a black, scab-like covering, described in the paper as a "crust." Many weeks after the crust fell off, the results were still unsettlingly poor:

- Two lesions were still visibly malignant (1c and 2c)

- One appeared relatively normal but remained cancerous (1d)
- Two developed seborrheic keratosis, a skin condition that resembles cancer (2d and 2e)
- Two developed what the authors described as "hyperpigmentation" (2a and 2b, shown above), as well as "dermal scar[s]"
- Two looked relatively normal but suffered from "dermal scar[s]" (1a and 1e)
- One looked relatively normal (1b)

Relative to Pulse's spin about offering a "scarless" alternative – as well as its long-term ambition to pursue other cosmetically sensitive dermatological indications – these outcomes are abysmal. Only one out of ten lesions treated can honestly be described as fixed.

Nor is "curing" 70% of the lesions (as measured just ~14 weeks after treatment) an impressive accomplishment. The gold standard for the treatment of basal-cell carcinoma, a technique called Mohs surgery, is extremely effective; among patients with primary BCC, i.e. those who have never had the cancer before, 99% are still cancer-free *five years* after treatment (20). In the NPS trial, by contrast, just one out of three patients was cancer-free within a matter of months; we'll likely never know the longer-term recurrence rate, but it can only get worse. While other treatments are less effective than Mohs surgery, none is nearly as bad as Pulse's NPS:

Nano-Pulse Stimulation Appears to Be the Worst Known Treatment for Basal-Cell Carcinoma

Treatment method	5-year recurrence rate for primary BCC
Mohs surgery	1%
Standard surgical excision	5-10%
Curettage and electrodessication	7-13%
Radiation	7-9%
Cryotherapy	8%
Pulse's NPS	**30%+**

Source: Kauvar et al. 2015 (20)*, Nuccitelli et al. 2014* (4)*, Kerrisdale analysis*

While Pulse (then BioElectroMed) didn't acknowledge the inferiority of its results – "The efficacy of this treatment modality was good," it bizarrely insisted – it did make excuses. Some of the lesions could only be partially ablated, the authors claimed, because they were larger than the NPS system's electrodes. But these lesions were still quite small; the largest was just 2 cm x 1 cm (0.8 in x 0.4 in). Moreover, the researchers *did* attempt to cover the entirety of the lesions, splitting them into multiple regions and applying many pulses to each region; according to them, they simply failed to do a good enough job. But if implementing NPS is so difficult and impractical that even small skin lesions can overwhelm it, how can it possibly succeed in the

real world? Furthermore, what happened to the much vaunted immune response that NPS is supposed to trigger? As Pulse tells the tale, NPS is so powerful and immunogenic that ablating a tumor in one part of the body will prevent tumor growth in other parts. In the BCC trial, however, improved lesions and cancerous lesions co-existed; there was no sign that the former conferred any benefit upon the latter.

In short, in its clinical debut (and only published trial to date), Pulse's NPS technology badly underperformed all standard treatments for basal-cell carcinoma in terms of eradicating cancer, while also producing multiple unexpected and unexplained skin anomalies – and singularly failing to give any indication of positive immune benefit. It's no wonder that NPS has remained obscure.

NPS Fails to Kill Many Cancer Cells

In the wake of NPS's abysmal debut trial, researchers directly funded by Pulse[17] have very recently published another disturbing set of results. To gauge the sensitivity of different human cell types, both cancerous and healthy, to NPS, the researchers applied standardized treatment regimens *in vitro*. What they found was that the number of pulses it took to kill half the cells treated (the LD_{50}) varied massively, and for no discernible reason, across different cell types, with a factor of *80* separating the relevant dose for the most and least sensitive categories. Moreover, cancer cells were generally *less* sensitive to NPS – better able to survive it – than healthy cells, an obviously undesirable pattern for a putative cancer treatment.

While the unpredictability and inconsistency of NPS is itself problematic, the most alarming finding – what the authors called "yet another unexpected characteristic of the survival curves" – was the phenomenon of residual resistivity: even after thousands of pulses, a meaningful fraction (10-20%) of populations of every type of cell tested continued to survive. While similar examples of incomplete killing had been reported before, the authors had chalked them up to methodological flaws. Here, however, they took great pains to remove all sources of doubt yet upheld their initial conclusion (emphasis added):

> We were able to find isolated live cells…even after the most intense treatments…[R]esidual resistivity was not an artifact but reflected an unusual level of nsPEF tolerance in a limited sub-population of cells. Understanding the mechanism underlying this tolerance, as well as methods to overcome it, is essential for efficient tumor ablation by nsPEF and remains an area for future investigation.
>
> …[The data] provided evidence for the highly diverse nsPEF sensitivity not only between cell lines, but also between individual cells within each cell line. **The presence of these resistant cells could have a major impact on the successful ablation of tumors**,

[17] See Gianulis et al. 2017's acknowledgements: "This work was supported by a Grant from Pulse Biosciences Inc.…"

> thus stressing the need to identify the physiological characteristics responsible for nsPEF tolerance.

Though couched in staid academic language, these words mark a crisis in Pulse's research agenda. When 10-20% of neuroblastoma cells, liver-cancer cells, fibrosarcoma cells, and pancreatic-cancer cells survive "even after the most intense" NPS exposure, the notion of NPS as a universal cancer-treatment "platform" becomes absurd. Zapping away a fraction of a tumor won't do much good when the resistant remainder can rapidly grow back. Nor is there good reason to expect that Pulse researchers can quickly solve this problem; after all, as described in the paper, they already tested many possible explanations but failed to find one that fit the facts.

Stepping back, it should come as no surprise that a tumor-ablation modality that purportedly relies on apoptosis would falter. After all, in order to become cancerous in the first place, cells must be able to overcome natural checks on aberrant growth, including apoptosis; as tumors grow, pro-apoptotic mechanisms tend to weaken and fail (21). By contrast, it's difficult for cells to resist physical interventions like freezing temperatures or scalpels. There is thus good reason to believe that the latest finding of Pulse's own research – that many cells, both healthy and cancerous, cannot be killed by NPS – will stand the test of time and render its technology worthless.

V. Conclusion

Pulse is a tiny company that has made virtually no progress toward commercializing a technology that barely seems to work in the first place – yet the market is pricing it as if it were already 13x more valuable than its closest peer. In the years to come, Pulse will need to repeatedly raise capital to cover its cash outflows as it attempts to inch closer to becoming a real business. But we believe this money will be wasted: Pulse's NPS technology is simply too similar to NanoKnife's irreversible electroporation to gain much traction, especially when the best available evidence reveals NPS to be ineffective and unreliable. These nanosecond pulses deserve a nanocap valuation, at least 90% lower than where Pulse trades today.

References

1. *Improved Local and Systemic Anti-Tumor Efficacy for Irreversible Electroporation in Immunocompetent versus Immunodeficient Mice.* **Neal, Robert E. II, et al.** 5, May 2013, PLoS ONE, Vol. 8, p. e64559.
2. *Irreversible Electroporation (IRE) Fails to Demonstrate Efficacy in a Prospective Multicenter Phase II Trial on Lung Malignancies: The ALICE Trial.* **Ricke, Jens, et al.** 2, 2015, Cardiovasc Intervent Radiol, Vol. 38, pp. 401-8.
3. *A Randomized Trial Comparing Radiofrequency Ablation and Surgical Resection for HCC Conforming to the Milan Criteria.* **Huang, Jiwei, et al.** 6, December 2010, Annals of Surgery, Vol. 252, pp. 903-912.
4. *First-in-human trial of nanoelectroablation therapy for basal cell carcinoma: proof of method.* **Nuccitelli, Richard, et al.** 2014, Experimental Dermatology, Vol. 23, pp. 130-142.
5. *Selective susceptibility to nanosecond pulsed electric field (nsPEF) across different human cell types.* **Gianulis, Elena C., et al.** 2017, Cellular and Molecular Life Sciences, Vol. 74, pp. 1741-1754.
6. *Focal irreversible electroporation for prostate cancer: functional outcomes and short-term oncological control.* **Ting, F, et al.** March 2016, Prostate Cancer and Prostatic Diseases, Vol. 19, pp. 46-52.
7. *High-Frequency Irreversible Electroporation: Safety and Efficacy of Next-Generation Irreversible Electroporation Adjacent to Critical Hepatic Structures.* **Siddiqui, Imran A., et al.** 2017, Surgical Innovation, pp. 1-8.
8. *Calcium-Mediated Pore Expansion and Cell Death Following Nanoelectroporation.* **Pakhomova, Olga N., et al.** 2014, Biochimica et Biophysica Acta, Vol. 1838, pp. 2547-2554.
9. **Westhoff, Mike-Andrew, Marschall, Nicolas and Debatin, Klaus-Michael.** Novel Approaches to Apoptosis-Inducing Therapies. [ed.] Christopher D. Gregory. *Apoptosis in Cancer Pathogenesis and Anti-Cancer Therapy*. 2016, pp. 173-204.
10. *Thermal Albation of Tumours: Biological Mechanisms and Advances in Therapy.* **Chu, Katrina F. and Dupuy, Damian E.** March 2014, Nature Reviews Cancer, Vol. 14, pp. 199-208.
11. *Cryo-Immunology: A Review of the Literature and Proposed Mechanisms for Stimulatory versus Suppressive Immune Responses.* **Sabel, Michael S.** 2009, Cryobiology, Vol. 58, pp. 1-11.
12. *Harnessing the Immunomodulatory Effect of Thermal and Non-Thermal Ablative Therapies for Cancer Treatment.* **Bastianpillai, Christopher, et al.** 12, September 2015, Tumor Biology, Vol. 36, pp. 9137-9146.
13. *Immunogenic Cell Death in Cancer and Infectious Disease.* **Galluzzi, Lorenzo, et al.** 2017, Nature Reviews Immunology, Vol. 17, pp. 97-111.
14. *Antitumor Effect after Radiofrequency Ablation of Murine Hepatoma Is Augmented by an Active Variant of CC Chemokine Ligand 3/Macrophage Inflammatory Protein-1α.* **Iida, Noriho, et al.** 2010, Cancer Research, Vol. 70, pp. 6556-6565.
15. *Immune Adjuvant Activity of Pre-Resectional Radiofrequency Ablation Protects against Local and Systemic Recurrence in Aggressive Murine Colorectal Cancer.* **Ito, Fumito, et al.** November 2015, PLoS One.

16. *Effects of high-intensity focused ultrasound in the treatment of experimental neuroblastoma.* **Yang, Rong, et al.** 2, 1992, Journal of Pediatric Surgery, Vol. 27, pp. 246-251.
17. *Thermal and Mechanical High-Intensity Focused Ultrasound: Perspectives on Tumor Ablation, Immune Effects and Combination Strategies.* **van den Bijgaart, Renske J.E., et al.** 2, 2017, Cancer Immunology, Immunotherapy, Vol. 66, pp. 247-258.
18. *Irreversible Electroporation versus Radiofrequency Ablation: A Comparison of Local and Systemic Effects in a Small-Animal Model.* **Bulvik, Baruch E., et al.** 2, August 2016, Radiology, Vol. 280, pp. 413-424.
19. *In vitro and in vivo evaluation and a case report of intense nanosecond pulsed electric field as a local therapy for human malignancies.* **Gardon, Edward B., et al.** 2007, Int. J. Cancer, Vol. 121, pp. 675-682.
20. *Consensus for Nonmelanoma Skin Cancer Treatment: Basal Cell Carcinoma, Including a Cost Analysis of Treatment Methods.* **Kauvar, Arielle N.B., et al.** 5, May 2015, Dermatol Surg, Vol. 41, pp. 550-571.
21. *Radiation-Induced Cell Death Mechanisms.* **Eriksson, David and Stigbrand, Torgny.** 2010, Tumor Biol, Vol. 31, pp. 363-372.
22. *Study of Apoptosis and Heat Shock Protein (HSP) Expression in Hepatocytes Following Radiofrequency Ablation (RFA).* **Rai, R., et al.** 1, November 2005, Journal of Surgical Research, Vol. 129, pp. 147-151.

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