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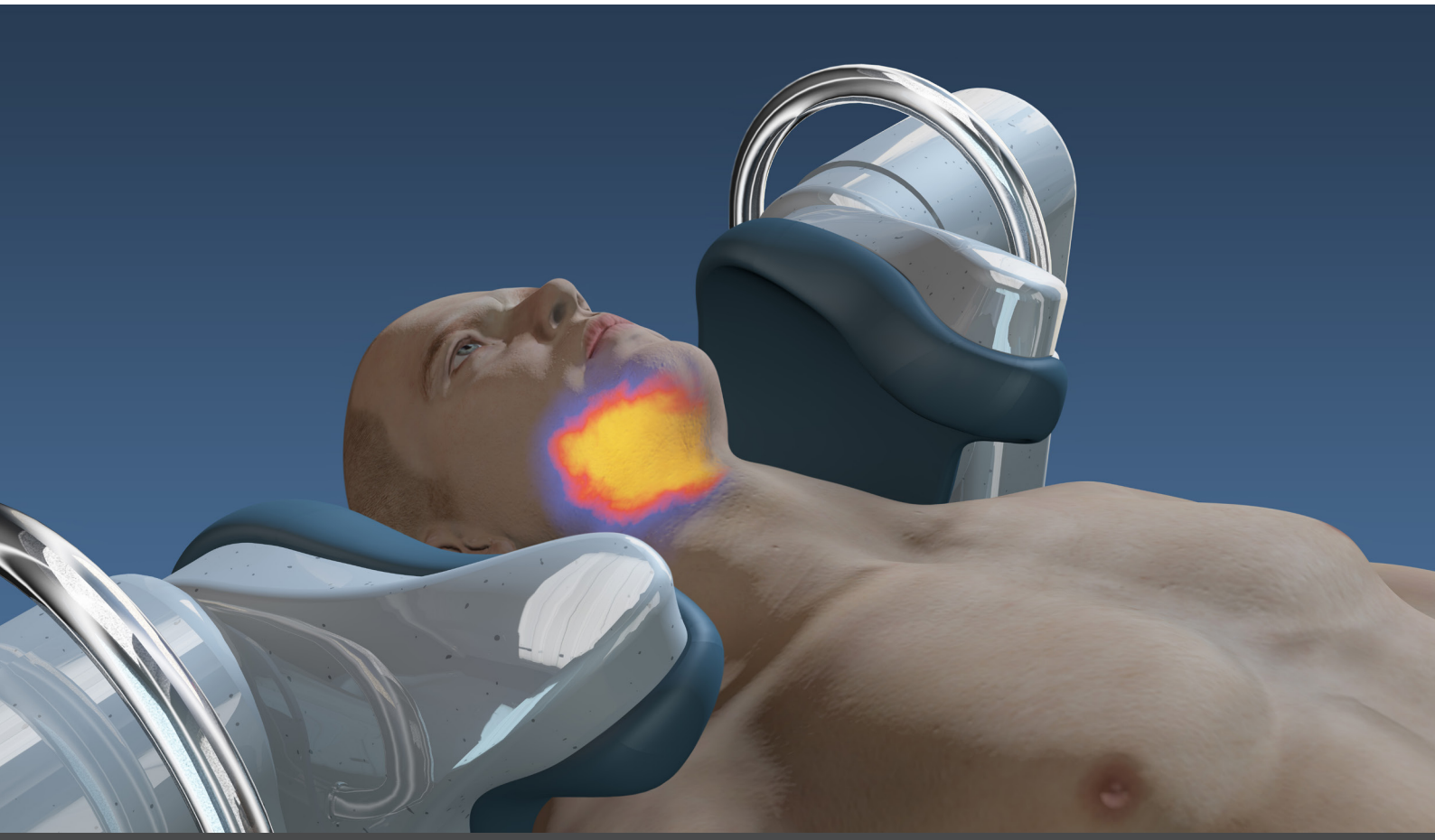

Heating of solid tumours

in conjunction with mainstream treatments

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Heating of solid tumours in conjunction with mainstream treatments.

In multiple phase III trials (i.e. Level 1 evidence) a better clinical outcome has been demonstrated for the combination of hyperthermia[1] with mainstream therapies versus mainstream therapies alone. Since then, Sensius and other companies have developed a novel state of the art tumour-heating system that promises more patient comfort and even better clinical outcomes.

In order to achieve efficacy and less toxicity, the treatment must be defined on a scientific and technological basis. Sensius focuses on controlled energy distribution. The energy is focused to the target volume and the risk of a too high temperature in surrounding vulnerable tissue is negligible. Blood flow around the tumour has a high impact on the temperature distribution. The blood flow is mostly unmapped and temperature dose dependent. By our focus on the energy deposition, we create the best result on temperature. Thus, the patient experiences better outcome and less toxicity and hence, a better Quality of Life.

Sensius developed a protocol for controlled treatment. Upon CT/MRI patient scanning, a three dimensional model of the tumour and surrounding tissues is being generated. After simulation and optimization of heat distribution, the actual treatment of the patient takes place. The technology for conveying controlled energy lies in the use of smart antenna arrays. Because of the high level of computerization and standardization, the preparation time amounts to just one hour. The therapy is for patients relatively comfortable and amounts to less than two hours per treatment.

In summary, Sensius developed a complete chain of integrated operations by a multidisciplinary team, from CT/MRI patient scanning till the application of smart antenna arrays. In order to differentiate our defined and standardized treatment from the myriad of hyperthermia applications, we call our approach 'Thermotherapy'. For the patient this means more comfort and a higher Quality of Life.

So, applying thermotherapy, Sensius enables the clinical oncologist to choose between two strategies:

a) A better clinical outcome with the same toxicity, or
b) The same clinical outcome with less toxicity because of the option to minimize exposure to radiation (or chemo).

This allows a patient tailored treatment to achieve the balance between clinical outcome and quality of life.

[1] For the Biology and Underlying Mechanisms of Actions by Hyperthermia, see attachment 1.

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ATTACHMENT 1

Biology and Underlying Mechanisms of Actions by Hyperthermia

A. Macroscopic level, Mechanism of Action.

The tumour microenvironment often has poorly vascularized regions, leading to a diminished blood supply. This causes the presence of hypoxic, acidic and nutrient-deprived regions, which are responsible for the low effectiveness of radiotherapy and chemotherapy in these regions.

Mild heat treatment changes these characteristics. This leads to normalization of oxygen, nutrient and pH levels. The enhanced tumour perfusion and oxygenation are the predominant biological mechanisms by which mild heat treatment improves chemo and radiotherapeutic tumour killing effectiveness. This is because the higher oxygen concentration makes the formation of reactive oxygen species (ROS) possible which sensitizes the tumour cells towards chemo- and radiotherapy.

There is consensus on mechanisms. The pathways are understood. It has been positively demonstrated in Human applications of hyperthermia.

B. Microscopic level:

- **Systemic and Local Immunostimulatory effects.**
  Scientific data suggest local and systemic effects of mild heat treatment exist because of boosting antitumour immunity. This is based on many immunological effects, amongst those: increase of the presence of immune cells due to vascular effects; formation of Heat Shock Protein 70 (HSP70) which stimulates Dendritic Cell (DC) mediated immune response and infiltration of Natural Killer (NK) and other T- cells.

- **Cellular Level: DNA repair mechanisms**
  Homologous recombination is a repair process used by tumour cells facing DNA double strand breaks. BRCA2 is a major component of the homologous repair system. Mild heat treatment has been shown to effectively inhibit homologous DNA repair by degradation of BRCA2.

Many immunological pathways and mechanisms regarding hyperthermia on microscopic level have been discovered. The effects so far have been found in mice/rats and on cellular level by *in vitro* experiments.

Please Note: An animation explaining the biology and underlying mechanisms of action by hyperthermia can be found on this page:

https://www.sensiusthermotherapy.com/state-of-the-art/mechanism-of-action-video-mild-heat-treatment/

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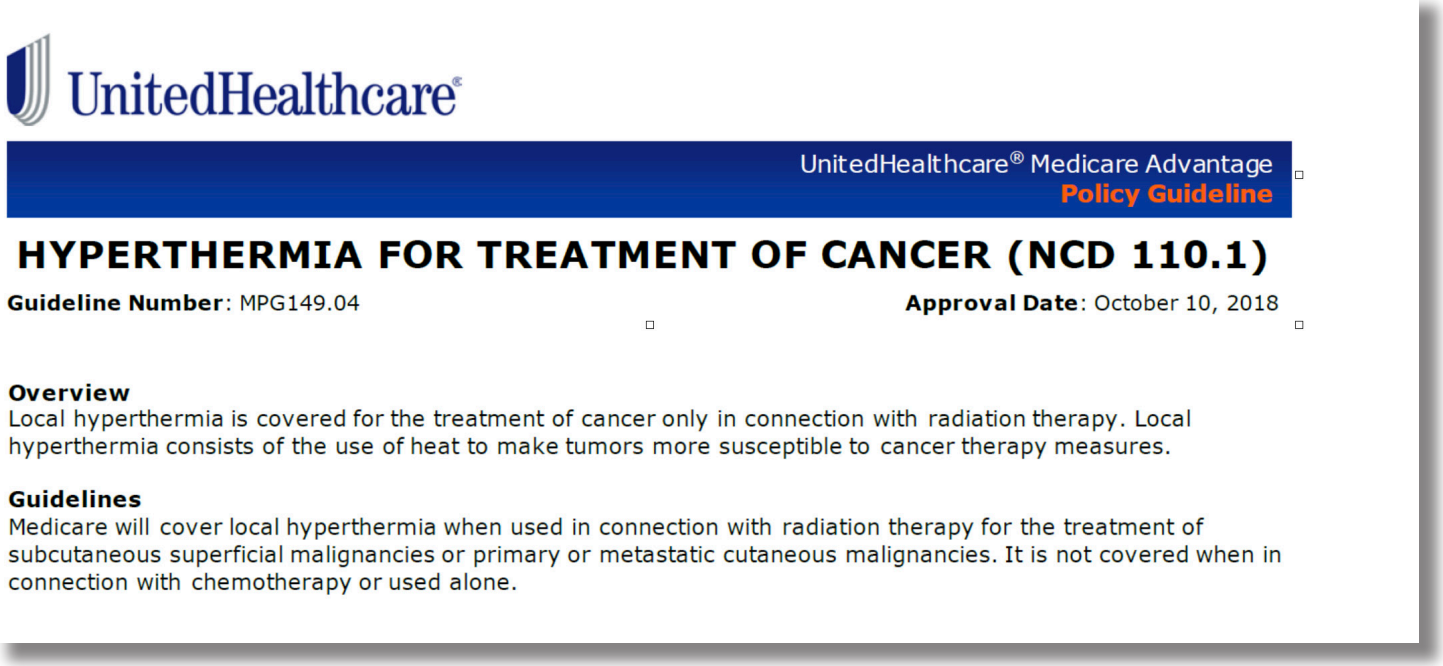
ATTACHMENT 2

Tentative reimbursement overview

A. Reimbursement in the US.

The market proliferation will strongly depend on reimbursement status. Hospitals will carry out thermotherapy on a commercial scale once reimbursement is in place. A summary of the current reimbursement situation in the USA is shown here.



UnitedHealthcare®

UnitedHealthcare® Medicare Advantage
Policy Guideline

HYPERTHERMIA FOR TREATMENT OF CANCER (NCD 110.1)

Guideline Number: MPG149.04 **Approval Date**: October 10, 2018

Overview
Local hyperthermia is covered for the treatment of cancer only in connection with radiation therapy. Local hyperthermia consists of the use of heat to make tumors more susceptible to cancer therapy measures.

Guidelines
Medicare will cover local hyperthermia when used in connection with radiation therapy for the treatment of subcutaneous superficial malignancies or primary or metastatic cutaneous malignancies. It is not covered when in connection with chemotherapy or used alone.

Special reimbursement rules for Deep Regional Hyperthermia.
The Institutional Review Board (IRB) approved Humanitarian Use Device (HUD) Exemption Inclusion Criteria.

- Histologically proven advanced, persistent or recurrent deep tumor of the pelvis and abdomen; for example being, sarcoma, renal ca., pancreatic ca., cervical/endometrial, prostate, rectum, colon or bladder.
- Concurrent Disease - Patients under treatment for concurrent medical conditions will be eligible for protocol treatment if, in the opinion of the physician responsible for hyperthermia treatment that the concurrent medical condition will neither interfere with the process of the treatment or patient assessments nor add significantly to the risks or complications of the treatment. This assessment and final conclusion should be documented within the patient's medical records.

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Status summary

B. Reimbursement in Europe.

The status of the reimbursement varies per country, from clinics engaged for trials up to reimbursement in place for specific tumour pathologies.

Country	Reimbursement status summary	Route
Germany	Tumour indications under reimbursement: recurrent breast cancer in previously irradiated areas, soft tissue sarcoma, rectum tumours, cervix cancer, various recurrent tumours.	Roadmap for Deep HT for primary tumours; includes Clinical trials which are in place.
Switzerland	Reimbursed/Under evaluation: • HT with concurrent re-irradiation for curative indications and for tumours in specific anatomic areas. • Selected palliative indications both for superficial and deep locations. • For specific soft tissues sarcomas: CT and HT, Protontherapy and HT.	Hospitals (Oncological Network) take care of reimbursement procedures.
Netherlands	Reimbursement in place for hyperthermia in combination with radiotherapy. Regional deep and superficial hyperthermia, e.g. tumours that are recurrent in previously irradiated areas. Hyperthermic Intraperitoneal Chemotherapy: e.g. types of colon cancer, mesothelioma, ovarian cancer and HIVEC.	Roadmap for Deep HT for primary tumours; includes Clinical trials which are in place.

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ATTACHMENT 3

Glossary

- BRCA2 is part of a complex that acts directly in double-strand break DNA repair. Such a double strand break can occur after radiation therapy. Upon temperature increase to 42 ^{O}C, BRCA2 disappears, thereby impeding the DNA repair mechanism.

- Clinical oncologist is a doctor who treats cancer and provides medical care for a person diagnosed with cancer. A clinical oncologist may also be called a cancer specialist.

- Dendritic Cells: In the context as described here, dendritic cells are confronted with proteins that are generated by the process of thermotherapy. Subsequently these dendritic cells are presenting these proteins to the immune system in order to influence the outcome of the immune system.

- Heat Shock Protein 70 (HSP70): a member of the family of proteins produced by cells in response to exposure to stress conditions. Under thermotherapy conditions these proteins stabilize other proteins to prevent damage. There are many heat shock proteins, HSP70 is one of the most widely studied.

- Homologous Recombination. DNA damage is a fact of life as a consequence of endogenous sources and processes as well as exogenous sources, for example radiation therapy.
  To repair DNA damage, Homologous Recombination plays a prominent role in faithfully duplicating the genome by providing critical support for DNA replication.

- IRB. Under FDA regulations, an Institutional Review Board is a group that has been formally designated to review and monitor biomedical research involving human subjects. In accordance with FDA regulations, an IRB has the authority to approve, require modifications in (to secure approval), or disapprove research.

- Mainstream therapies are Radiotherapy, chemotherapy, immune therapy and surgery.

- Natural Killer Cells are part of the family of white blood cells. Their function is to destroy infected and diseased cells, like cancer cells.

- ROS: Reactive oxygen species (ROS) are molecules capable of independent existence, containing at least one oxygen atom and one or more unpaired electrons. This group includes oxygen free radicals. In Radiotherapy, radiation interacts with water molecules to form H2O+ and a free electron. These products then react with another water molecule to form highly active •OH or other ROS species. ROS directly damage biomolecules, such as lipids, proteins and DNA.

- SAR means Specific Absorption Rate and the meaning is the amount of energy that is applied per weight of tumour.

- T-cells are part of the family of white blood cells. There are two major subtypes: helper T-cells and killer T-cells.

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ATTACHMENT 4

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