Cancer Association of South Africa (CANSA)

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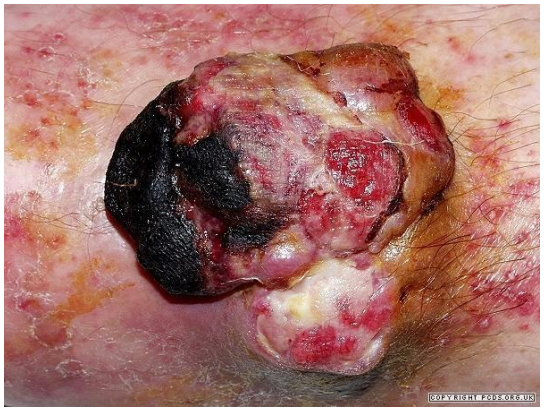
Fact Sheet on Leiomyosarcoma

Introduction

Leiomyosarcoma (LMS) is a type of soft tissue sarcoma. Soft tissue sarcoma is a cancer that starts in soft tissues of the body, including muscle, tendons, fat, lymph vessels, blood vessels, nerves, and tissue around joints. The tumours can be found anywhere in the body but often form in the arms, legs, chest, or abdomen. Soft tissue sarcomas can develop in muscle, fat, blood vessels, or any of the other tissues that support, surround and protect the organs of the body.



[Picture Credit: Subcutaneous Leiomyosarcoma]

Both children and adults can develop soft tissue sarcoma. Treatment often works better in children and they may have a better chance of being cured than adults. There are many types of soft tissue sarcoma, based on the type of soft tissue cell in which the cancer formed. Different types may be treated differently.

Leiomyosarcoma (LMS) is one of the more common types of soft tissue sarcoma to develop in adults. The exact cause of LMS is not yet known.
(MacMillan Cancer Support; National Cancer Institute).

Types of Leiomyosarcoma (LMS)

Leiomyosarcoma, or LMS is a rare condition and yet there are a few thousand cases each year all over the world. It is a form of soft tissue cancer and appears specifically in the involuntary muscles. Now, that is a very simplified explanation of it, but it does say one thing in particular – it can appear almost anywhere. This is because the blood vessels of the body have soft tissue and involuntary muscles. Thus, one can develop LMS in the lining of organs, and anywhere blood vessels appear.

There are three types of LMS:

Somatic Soft Tissue LMS - the words “somatic soft tissue” are another way of describing the body’s connective tissue. This is the most common location for LMS to appear, and so almost everyone diagnosed with LMS may be said to have LMS of the somatic soft tissue.

Interestingly enough, the somatic soft tissues hold the body together, but they are not the same tissues as those of the organs (such as the kidneys). Although one's liver or kidneys can be called soft tissue, when cancers are due to something malfunctioning in the actual cells that make up one's visceral organs, they are not sarcomas. Those are known as carcinomas instead. So, someone who has liver cancer is not, necessarily, someone with LMS.

Cutaneous or Subcutaneous LMS - this is a very rare form of LMS and is when the "pilo erector" muscles in the skin develop the condition. It is often viewed as a dermatological condition in addition to something for an oncologist. Fortunately, for someone diagnosed with the cutaneous version there is an "excellent outcome with rare recurrence". For the subcutaneous variants, though, treatment can be challenging.

LMS of a Vascular Origin - noted as truly rare, however, it has occurred. This is when LMS comes directly from a major blood vessel such as the inferior vena cava. Additionally, the pulmonary artery can be involved along with peripheral arteries. There are formal syndromes that arise from some of these variants of LMS due to the symptoms and issues they may cause. For example, Budd-Chiari syndrome is what presents in those with LMS in the inferior vena cava.

Other LMS Variants - experts indicated that there are also cases of LMS in those with immunocompromised conditions and even LMS of the bone. Additionally, the patient with gastrointestinal tumours once cited as a form of LMS will no longer be identified as such. Instead, this is now known as GISTs or Gastrointestinal Stromal Tumours. These are no longer viewed as a form of LMS and though they are tumours of the smooth tissue and muscles of the stomach, they are treated with a unique and initially successful new drug protocol.
(Sarcoma).

Incidence of Leiomyosarcoma in South Africa
The National Cancer Registry (2012) does not make any mention of the incidence of Leiomyosarcoma in South Africa.

General Clinical Features of LMS
There are no specific clinical features diagnostic of leiomyosarcoma of soft tissue that distinguish these tumours from other soft tissue sarcomas. Women are affected more than men, with the disease typically occurring in the 5th and 6th decades of life. This gender distribution may reflect the proliferation of smooth muscle that can occur in response to oestrogen. Prognosis and treatment varies on the location, stage and grade of the primary tumour as well as the presence of metastatic disease. The most common site of involvement of leiomyosarcoma is the retroperitoneum, accounting for approximately 50% of occurrences.[8] In the case of retroperitoneal tumours, presenting signs and symptoms can include an abdominal mass, pain, swelling, weight loss, nausea or vomiting. Leiomyosarcoma of somatic soft tissues, like other soft tissue sarcomas, often present as an enlarging, painless mass. Although these tumours are generally associated with small blood vessels, they usually do not present with signs or symptoms of vascular compression. However, when leiomyosarcoma arises from a major blood vessel, symptoms of vascular compromise or leg oedema may be present, as well as neurologic symptoms such as

numbness from compression of an adjacent nerve. Soft tissue leiomyosarcoma typically affects adults, however it can present in childhood.
(The Liddy Shriver Sarcoma Initiative).

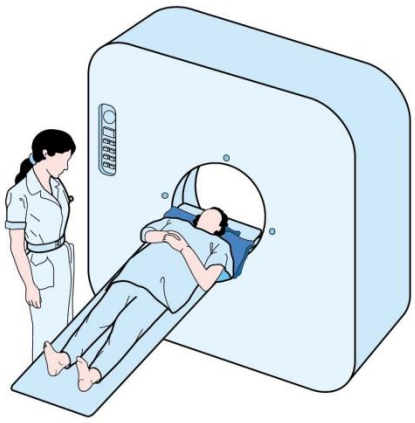
Diagnosis of Leiomyosarcoma (LMS)
Ultrasound examination, magnetic resonance imaging (MRI), or computed tomography (CT) do not reliably distinguish between sarcoma, leiomyoma, endometrial cancer, lymphoma, intravenous leiomyomatosis, or adenomyosis.

The following tests are commonly used to diagnose a leiomyosarcoma. The tests one has will depend on the part of the body being investigated. One may have had some of these tests already.

Hysteroscopy - this test is used to diagnose problems in the uterus (womb). The doctor uses a small, thin tube with a light and camera at the end (hysteroscope) to look into the womb and takes tissue samples (biopsies) to be looked at under a microscope. The hysteroscope is passed through the vagina and into the womb. One may have this test as an outpatient under local anaesthetic, but sometimes a general anaesthetic is needed.
A hysteroscopy may be uncomfortable but should not be painful. Some women may have mild cramping during the procedure and for a few days afterwards. It is advised to take mild painkillers, such as paracetamol, 30 minutes before the procedure.

Ultrasound scan - this test uses sound waves to create a picture of the abdomen and surrounding organs. It is done in the hospital's scanning department. One will be asked not to eat, and to drink only clear fluids (nothing fizzy or milky) for 4-6 hours before the scan.
Once lying comfortably on one's back, a gel is spread over the abdomen. A small device like a microphone (called a probe) is then rubbed over the area. It emits sound waves that are then converted into a picture using a computer. The test should not be painful and takes about 15-20 minutes.
If a uterine sarcoma is suspected, the probe will also be inserted gently into the vagina to examine the uterus (womb) more closely.
Ultrasound may also be used to look for a suspected cancer in a limb.

CT (computerised tomography) scan - a CT scan takes a series of x-rays, which build up a three-dimensional picture of the inside of the body. The scan takes 10–30 minutes and is painless. It uses a small amount of radiation, which is very unlikely to harm either the patient nor harm anyone he/she comes into contact with. The patient is asked not to eat or drink for at least four hours before the scan.



CT scan one may be given a drink or injection of a dye, which allows particular areas to be seen more clearly. This may make one feel hot all over for a few minutes. It is important to let the doctor know if one is allergic to iodine or have asthma, because one could have a more serious reaction to the injection.

Patients are usually able to go home as soon as the scan is over.

MRI scan - this test uses magnetism to build up a detailed picture of areas of the body. The scanner is a powerful magnet so one is asked to complete and sign a checklist to make sure it is safe. The checklist asks about any metal implants one may have, such as a pacemaker, surgical clips, bone pins, etc. One should also tell the doctor if one has ever worked with metal or in the metal industry as very tiny fragments of metal can sometimes lodge in the body. If one does have any metal in one's body it is likely that one will not be able to have an MRI scan. In this situation another type of scan can be used.

Before the scan, patients are asked to remove any metal belongings including jewellery. Some people are given an injection of dye into a vein in the arm, which does not usually cause discomfort. This is called a contrast medium and can help the images from the scan to show up more clearly. During the test the patient lies very still on a couch inside a long cylinder (tube) for about 30 minutes. It is painless but can be slightly uncomfortable, and some people feel a bit claustrophobic. It is also noisy, but patients are given earplugs or headphones. The patient can hear, and speak to, the person operating the scanner.

Biopsy - the results of the previous tests may make the doctor strongly suspect the patient has cancer. The only way to be sure is to take some cells or a small piece of tissue from the affected area to look at under a microscope. This is called a biopsy. The area is numbed using a local anaesthetic injection and then a fine needle is passed into the tumour through the skin. A CT or ultrasound scan may be used at the same time to make sure that the biopsy is taken from the right place. Sometimes the biopsy is taken during a hysteroscopy (see above).

When the cells are looked at under a microscope, the specialist will be able to tell whether they are benign (not cancerous) or malignant (cancerous). If a sarcoma is diagnosed, further tests may be done on the sample to try to find out exactly what type of sarcoma it is.
(MacMillan Cancer Support: The Liddy Shriver Sarcoma Initiative).

The Stages of Leiomyosarcoma (LMS)
Staging LMS means looking at the size of the tumour done during diagnosis, and looking to see if or how far it has spread beyond the original location. The most commonly used scale of stages is known as the AJCC system and it uses the grade, the size, the location, and signs of metastatic activity.

The staging uses a very simple alpha-numeric designation of mildest to most severe stages, and looks like this:

- 1A – low grade/less than 5cm in size/can be superficial or deep/no metastatic disease
- 1B – low grade/more or less than 5 cm in size/superficial/no metastatic disease
- 2A – low grade/more or less than 5 cm in size/deep/no metastatic disease
- 2B – high grade/less than 5 cm in size/can be superficial or deep/no metastatic disease
- 2C – high grade/more or less than 5 cm in size/superficial/no metastatic disease
- 3 – high grade/more or less than 5 cm in size/deep/no metastatic disease
- 4 – any grade/any size/any location/metastatic disease

With this system, a medical team can then design the most appropriate treatment and give their patient the most accurate prognosis. This sort of diagnosis is vital to combating LMS, and is the best step towards overcoming it.
(Sarcoma.org).

Table 1: AJCC staging system

Stage	Histological Grade	Size	Location (Relative to fascia)	Systemic / Metastatic Disease Present
IA	Low	< 5cm	Superficial or Deep	No
IB	Low	≥ 5cm	Superficial	No
IIA	Low	≥ 5cm	Deep	No
IIB	High	< 5cm	Superficial or Deep	No
IIC	High	≥ 5cm	Superficial	No
III	High	≥ 5cm	Deep	No
IV	Any	Any	Any	Yes

Table 2: MSTS Staging system

Stage	Histological Grade	Local Extent of Disease	Systemic / Metastatic Disease Present
Ia	Low	Confined	No
Ib	Low	Unconfined	No
Ia	High	Confined	No
Ib	High	Unconfined	No
III	Any	Any	Yes

(Sarcomahelp.org).

Treatment of Leiomyosarcoma (LMS)
Due to the rarity of these tumours, and the need for a multi-specialty treatment team, treatment is best carried out in a specialized centre with expertise in sarcoma care. At our institution, treatment planning begins with a multi-disciplinary review of the patient's history, all available radiographic imaging, and the pathologic results from biopsy. A treatment plan is then formulated based upon the input from orthopaedic and general surgeons, musculoskeletal radiologists, pathologists, medical oncologists, and radiation oncologists.

Surgery - Local control of soft tissue sarcomas is usually achieved with surgical resection. Pre-operative planning based upon radiographic and pathologic information is important to ensure adequate surgical margins. Achieving wide surgical margins is important in preventing local recurrence.

Radiation Therapy - Many tumours involve or are directly adjacent to vital structures. In these cases achieving a wide surgical margin is impossible. Radiation therapy is an important additional treatment for improving rates of local control when surgical margins are close, especially in high-grade sarcomas. Radiation therapy can be delivered either pre-operatively (neoadjuvant) or post-operatively (adjuvant). Radiation therapy can also be utilized as a means of palliative local control in cases where extensive metastasis has already occurred.

Chemotherapy - The primary role of chemotherapy is in the treatment of metastatic disease. While not curative, it may slow the progression of systemic disease. Agents that are used in some sarcoma centres include: doxorubicin and ifosfamide, gemcitabine and taxotere (docetaxel), dacarbazine, and ecteinascidin. There are currently investigational studies underway to identify other agents that may prove useful in the treatment of leiomyosarcoma. Chemotherapy is sometimes used as an adjuvant in the treatment of localised sarcomas. No clear survival benefit has been demonstrated in retroperitoneal leiomyosarcomas. However, pre-operative chemotherapy may help to shrink a tumour away from vital structures, and improve the ability of surgeons to successfully remove a large tumour. In localized leiomyosarcoma of the extremities, there may be a survival benefit for adjuvant chemotherapy using doxorubicin-based regimens. Both retrospective and prospective studies have shown a benefit for neoadjuvant doxorubicin and ifosfamide based regimens in patients with large (>8cm) high-grade sarcomas.
(Sarcomahelp.org).

About Clinical Trials

Clinical trials are research studies that involve people. These studies test new ways to prevent, detect, diagnose, or treat diseases. People who take part in cancer clinical trials have an opportunity to contribute to scientists' knowledge about cancer and to help in the development of improved cancer treatments. They also receive state-of-the-art care from cancer experts.

Types of Clinical Trials

Cancer clinical trials differ according to their primary purpose. They include the following types:

Treatment - these trials test the effectiveness of new treatments or new ways of using current treatments in people who have cancer. The treatments tested may include new drugs or new combinations of currently used drugs, new surgery or radiation therapy techniques, and vaccines or other treatments that stimulate a person's immune system to fight cancer. Combinations of different treatment types may also be tested in these trials.

Prevention - these trials test new interventions that may lower the risk of developing certain types of cancer. Most cancer prevention trials involve healthy people who have not had cancer; however, they often only include people who have a higher than average risk of developing a specific type of cancer. Some cancer prevention trials involve people who have had cancer in the past; these trials test interventions that may help prevent the return (recurrence) of the original cancer or reduce the chance of developing a new type of cancer.

Screening - these trials test new ways of finding cancer early. When cancer is found early, it may be easier to treat and there may be a better chance of long-term survival. Cancer

screening trials usually involve people who do not have any signs or symptoms of cancer. However, participation in these trials is often limited to people who have a higher than average risk of developing a certain type of cancer because they have a family history of that type of cancer or they have a history of exposure to cancer-causing substances (e.g., cigarette smoke).

Diagnostic - these trials study new tests or procedures that may help identify, or diagnose, cancer more accurately. Diagnostic trials usually involve people who have some signs or symptoms of cancer.

Quality of life or supportive care - these trials focus on the comfort and quality of life of cancer patients and cancer survivors. New ways to decrease the number or severity of side effects of cancer or its treatment are often studied in these trials. How a specific type of cancer or its treatment affects a person's everyday life may also be studied.

Where Clinical Trials are Conducted

Cancer clinical trials take place in cities and towns in doctors' offices, cancer centres and other medical centres, community hospitals and clinics. A single trial may take place at one or two specialised medical centres only or at hundreds of offices, hospitals, and centres.

Each clinical trial is managed by a research team that can include doctors, nurses, research assistants, data analysts, and other specialists. The research team works closely with other health professionals, including other doctors and nurses, laboratory technicians, pharmacists, dieticians, and social workers, to provide medical and supportive care to people who take part in a clinical trial.

Research Team

The research team closely monitors the health of people taking part in the clinical trial and gives them specific instructions when necessary. To ensure the reliability of the trial's results, it is important for the participants to follow the research team's instructions. The instructions may include keeping logs or answering questionnaires. The research team may also seek to contact the participants regularly after the trial ends to get updates on their health.

Clinical Trial Protocol

Every clinical trial has a protocol, or action plan, that describes what will be done in the trial, how the trial will be conducted, and why each part of the trial is necessary. The protocol also includes guidelines for who can and cannot participate in the trial. These guidelines, called eligibility criteria, describe the characteristics that all interested people must have before they can take part in the trial. Eligibility criteria can include age, sex, medical history, and current health status. Eligibility criteria for cancer treatment trials often include the type and stage of cancer, as well as the type(s) of cancer treatment already received.

Enrolling people who have similar characteristics helps ensure that the outcome of a trial is due to the intervention being tested and not to other factors. In this way, eligibility criteria help researchers obtain the most accurate and meaningful results possible.

National and International Regulations

National and international regulations and policies have been developed to help ensure that research involving people is conducted according to strict scientific and ethical principles. In these regulations and policies, people who participate in research are usually referred to as "human subjects."

Informed Consent

Informed consent is a process through which people learn the important facts about a clinical trial to help them decide whether or not to take part in it, and continue to learn new information about the trial that helps them decide whether or not to continue participating in it.

During the first part of the informed consent process, people are given detailed information about a trial, including information about the purpose of the trial, the tests and other procedures that will be required, and the possible benefits and harms of taking part in the trial. Besides talking with a doctor or nurse, potential trial participants are given a form, called an informed consent form, that provides information about the trial in writing. People who agree to take part in the trial are asked to sign the form. However, signing this form does not mean that a person must remain in the trial. Anyone can choose to leave a trial at any time—either before it starts or at any time during the trial or during the follow-up period. It is important for people who decide to leave a trial to get information from the research team about how to leave the trial safely.

The informed consent process continues throughout a trial. If new benefits, risks, or side effects are discovered during the course of a trial, the researchers must inform the participants so they can decide whether or not they want to continue to take part in the trial. In some cases, participants who want to continue to take part in a trial may be asked to sign a new informed consent form.

New interventions are often studied in a stepwise fashion, with each step representing a different "phase" in the clinical research process. The following phases are used for cancer treatment trials:

Phases of a Clinical Trial

Phase 0. These trials represent the earliest step in testing new treatments in humans. In a phase 0 trial, a very small dose of a chemical or biologic agent is given to a small number of people (approximately 10-15) to gather preliminary information about how the agent is processed by the body (pharmacokinetics) and how the agent affects the body (pharmacodynamics). Because the agents are given in such small amounts, no information is obtained about their safety or effectiveness in treating cancer. Phase 0 trials are also called micro-dosing studies, exploratory Investigational New Drug (IND) trials, or early phase I trials. The people who take part in these trials usually have advanced disease, and no known, effective treatment options are available to them.

Phase I (also called phase 1). These trials are conducted mainly to evaluate the safety of chemical or biologic agents or other types of interventions (e.g., a new radiation therapy technique). They help determine the maximum dose that can be given safely (also known as the maximum tolerated dose) and whether an intervention causes harmful side effects. Phase I trials enrol small numbers of people (20 or more) who have advanced cancer that cannot be treated effectively with standard (usual) treatments or for which no standard

treatment exists. Although evaluating the effectiveness of interventions is not a primary goal of these trials, doctors do look for evidence that the interventions might be useful as treatments.

Phase II (also called phase 2). These trials test the effectiveness of interventions in people who have a specific type of cancer or related cancers. They also continue to look at the safety of interventions. Phase II trials usually enrol fewer than 100 people but may include as many as 300. The people who participate in phase II trials may or may not have been treated previously with standard therapy for their type of cancer. If a person has been treated previously, their eligibility to participate in a specific trial may depend on the type and amount of prior treatment they received. Although phase II trials can give some indication of whether or not an intervention works, they are almost never designed to show whether an intervention is better than standard therapy.

Phase III (also called phase 3). These trials compare the effectiveness of a new intervention, or new use of an existing intervention, with the current standard of care (usual treatment) for a particular type of cancer. Phase III trials also examine how the side effects of the new intervention compare with those of the usual treatment. If the new intervention is more effective than the usual treatment and/or is easier to tolerate, it may become the new standard of care.

Phase III trials usually involve large groups of people (100 to several thousand), who are randomly assigned to one of two treatment groups, or “trial arms”: (1) a control group, in which everyone in the group receives usual treatment for their type of cancer, or 2) an investigational or experimental group, in which everyone in the group receives the new intervention or new use of an existing intervention. The trial participants are assigned to their individual groups by random assignment, or randomisation. Randomisation helps ensure that the groups have similar characteristics. This balance is necessary so the researchers can have confidence that any differences they observe in how the two groups respond to the treatments they receive are due to the treatments and not to other differences between the groups.

Randomisation is usually done by a computer program to ensure that human choices do not influence the assignment to groups. The trial participants cannot request to be in a particular group, and the researchers cannot influence how people are assigned to the groups. Usually, neither the participants nor their doctors know what treatment the participants are receiving.

People who participate in phase III trials may or may not have been treated previously. If they have been treated previously, their eligibility to participate in a specific trial may depend on the type and the amount of prior treatment they received.

In most cases, an intervention will move into phase III testing only after it has shown promise in phase I and phase II trials.

Phase IV (also called phase 4). These trials further evaluate the effectiveness and long-term safety of drugs or other interventions. They usually take place after a drug or intervention has been approved by the medicine regulatory office for standard use. Several hundred to several thousand people may take part in a phase IV trial. These trials are also known as post-marketing surveillance trials. They are generally sponsored by drug companies.

Sometimes clinical trial phases may be combined (e.g., phase I/II or phase II/III trials) to minimize the risks to participants and/or to allow faster development of a new intervention.

Although treatment trials are always assigned a phase, other clinical trials (e.g., screening, prevention, diagnostic, and quality-of-life trials) may not be labelled this way.

Use of Placebos

The use of placebos as comparison or "control" interventions in cancer treatment trials is rare. If a placebo is used by itself, it is because no standard treatment exists. In this case, a trial would compare the effects of a new treatment with the effects of a placebo. More often, however, placebos are given along with a standard treatment. For example, a trial might compare the effects of a standard treatment plus a new treatment with the effects of the same standard treatment plus a placebo.

Possible benefits of taking part in a clinical trial

The benefits of participating in a clinical trial include the following:

- Trial participants have access to promising new interventions that are generally not available outside of a clinical trial.
- The intervention being studied may be more effective than standard therapy. If it is more effective, trial participants may be the first to benefit from it.
- Trial participants receive regular and careful medical attention from a research team that includes doctors, nurses, and other health professionals.
- The results of the trial may help other people who need cancer treatment in the future.
- Trial participants are helping scientists learn more about cancer (e.g., how it grows, how it acts, and what influences its growth and spread).

Potential harms associated with taking part in a clinical trial

The potential harms of participating in a clinical trial include the following:

- The new intervention being studied may not be better than standard therapy, or it may have harmful side effects that doctors do not expect or that are worse than those associated with standard therapy.
- Trial participants may be required to make more visits to the doctor than they would if they were not in a clinical trial and/or may need to travel farther for those visits.

Correlative research studies, and how they are related to clinical trials

In addition to answering questions about the effectiveness of new interventions, clinical trials provide the opportunity for additional research. These additional research studies, called correlative or ancillary studies, may use blood, tumour, or other tissue specimens (also known as 'biospecimens') obtained from trial participants before, during, or after treatment. For example, the molecular characteristics of tumour specimens collected during a trial might be analysed to see if there is a relationship between the presence of a certain gene mutation or the amount of a specific protein and how trial participants responded to the treatment they received. Information obtained from these types of studies could lead to more accurate predictions about how individual patients will respond to certain cancer treatments, improved ways of finding cancer earlier, new methods of identifying people who have an increased risk of cancer, and new approaches to try to prevent cancer.

Clinical trial participants must give their permission before biospecimens obtained from them can be used for research purposes.

When a clinical trial is over

After a clinical trial is completed, the researchers look carefully at the data collected during the trial to understand the meaning of the findings and to plan further research. After a phase I or phase II trial, the researchers decide whether or not to move on to the next phase or stop testing the intervention because it was not safe or effective. When a phase III trial is completed, the researchers analyse the data to determine whether the results have medical importance and, if so, whether the tested intervention could become the new standard of care.

The results of clinical trials are often published in peer-reviewed scientific journals. Peer review is a process by which cancer research experts not associated with a trial review the study report before it is published to make sure that the data are sound, the data analysis was performed correctly, and the conclusions are appropriate. If the results are particularly important, they may be reported by the media and discussed at a scientific meeting and by patient advocacy groups before they are published in a journal. Once a new intervention has proven safe and effective in a clinical trial, it may become a new standard of care.
(National Cancer Institute).

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