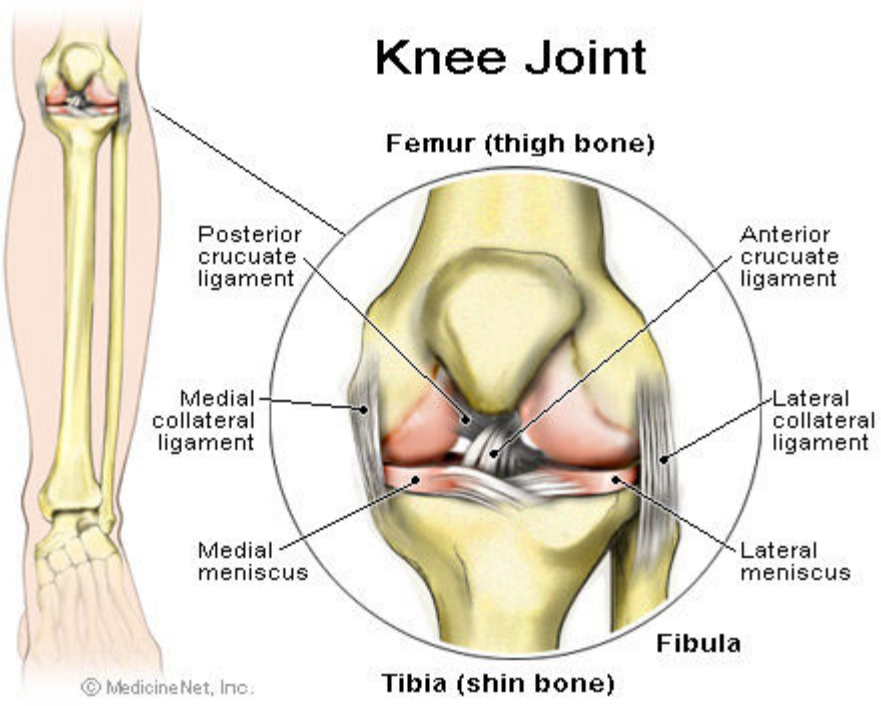
Knee and Joint Problems

How is the knee designed, and what is its function?

The knee is a joint which has three parts. The thigh bone (femur) meets the large shin bone (tibia) forming the main knee joint. This joint has an inner (medial) and an outer (lateral) compartment. The kneecap (patella) joins the femur to form a third joint, called the patellofemoral joint.

The knee joint is surrounded by a joint capsule with ligaments strapping the inside and outside of the joint (collateral ligaments) as well as crossing within the joint (cruciate ligaments). These ligaments provide stability and strength to the knee joint.

The meniscus is a thickened cartilage pad between the two joints formed by the femur and tibia. The meniscus acts as a smooth surface for the joint to move on. The knee joint is surrounded by fluid-filled sacs called bursae, which serve as gliding surfaces that reduce friction of the tendons. Below the kneecap, there is a large tendon (patellar tendon) which attaches to the front of the tibia bone. There are large blood vessels passing through the area behind the knee (referred to as the popliteal space). The large muscles of the thigh move the knee. In the front of the thigh, the quadriceps muscles extend the knee joint. In the back of the thigh, the hamstring muscles flex the knee. The knee also rotates slightly under guidance of specific muscles of the thigh.



The knee functions to allow movement of the leg and is critical to normal walking. The knee flexes normally to a maximum of 135 degrees and extends to 0 degrees. The bursae, or fluid-filled sacs, serve as gliding surfaces for the tendons to reduce the force of friction as these tendons move. The knee is a weight-bearing joint. Each meniscus serves to evenly load the surface during weight-bearing and also aids in disbursing joint fluid for joint lubrication.

Knee Injuries And Degeneration

The sort of swelling that occurs when a joint is damaged by injury or degeneration is normally essential to the healing process, but when it comes to the knee, that inflammation can actually interfere with healing.

These findings in experiments with pigs may lead to treatments for injuries or osteoarthritis in the knee, according to Duke University Medical Center orthopedic researchers. There are drugs that can block the action of these immune system proteins that trigger joint inflammation.

The Duke researchers report in the September issue of the journal *Arthritis & Rheumatism* that two immune system proteins, interleukin-1 (IL-1) and tumor necrosis factor (TNF), block the healing of the damaged pig meniscus, an important layer of buffering tissue within the joint. When agents that counteract the effects of these two proteins were administered directly to the damaged meniscus, the repair process resumed.

The primary function of the meniscus -- a type of cartilage located within the knee joint between the thigh bone (femur) and the lower leg bone (tibia) -- is to act as a shock absorber and a distributor of weight within the joint. Nearly 15 percent of all athletic injuries to the knee involve the meniscus, and the breakdown and loss of this tissue ultimately leads to osteoarthritis, the so-called "wear-and-tear" form of the disease.

The researchers, led by Duke postdoctoral fellow Amy McNulty, Ph.D., said there is a need for a new approach to treat these injuries. The most common meniscus injury is a tear. If the tear is small and occurs on the outside of the meniscus, it can be repaired surgically. However, these repairs don't often work well. If the tear is large, surgeons often have no choice but to remove the torn portion, and sometimes the entire meniscus, which leads to painful movement and ultimately osteoarthritis.

Duke researchers exposed pig knees to various concentrations of IL-1 and TNF. They found that as they increased the amounts of the proteins, the meniscus tissue was less able to repair itself. The range of concentrations of IL-1 and TNF used in the experiment match those found in the joint fluid of humans with rheumatoid arthritis and osteoarthritis, providing further evidence that these proteins could play a role in the disease process.

According to Farshid Guilak, Ph.D., senior member of the research team and director of orthopedic research at Duke, these findings

should theoretically help physicians repair knee joints damaged by injury or osteoarthritis.

"There already is a drug that blocks the effects of TNF that is used widely and effectively in patients with rheumatoid arthritis, the form of the disease caused by body's own immune system attacking the joint," Guilak said. "Another drug also exists that blocks IL-1 that is being used for rheumatoid arthritis and is currently undergoing clinical trials for osteoarthritis."

These drugs are administered to the entire body. However, the key to the possible new approach would be to deliver these agents directly into the site of meniscus damage, Guilak said.

Definition of Degenerative Joint Disease

Degeneration or 'wear and tear' of articular (joint surface) cartilage is usually accompanied by an overgrowth of bone (osteophytes), narrowing of the joint space, sclerosis or hardening of bone at the joint surface, and deformity in joints. OA is not usually associated with inflammation, although swelling of the joint does frequently occur in OA. This type of arthritis is called osteoarthritis, OA, degenerative joint disease, DJD, or osteoarthrosis. Other forms of arthritis (rheumatoid, post-traumatic, and other inflammatory disorders) frequently may have OA as the end-stage, making differentiation difficult.

Description of Degenerative Joint Disease

The tissues involved most in osteoarthritis are the cartilage and underlying subchondral bone. The cartilage is the smooth white material that forms over the ends of the bones and forms the moving surface of the joint on both sides. Cartilage is tough, elastic, very durable, and comprised of collagen and water molecules. Cartilage does not have a blood supply and receives its oxygen and nutrition from the surrounding joint fluid by diffusion. The ability of cartilage

to absorb nutrients and fluid allows it to function without a blood supply.
When we move a joint, the pressure across the joint expresses fluid and waste products out of the cartilage cells, and when the pressure is relieved, the fluid diffuses back, together with oxygen and nutrients. Hence the health of the cartilage depends on movement of the joint. Over many years and with activity and use of a joint, the cartilage may become frayed, injured, torn, and may even wear away entirely. When this occurs, the bone surface on one side of the joint tends to rub or glide against the bone on the opposite side of the joint, providing a less elastic joint surface, and generating higher contact pressures at the end of the bone. Over time, the contacting bone surfaces become hardened and 'sclerotic', a process that causes the bone to look polished and on x-rays produces a whitened appearance.

There are three common forms of osteoarthritis, and many people have some of each type. All people will develop OA to some degree, involving one or more joints, throughout their lifetime as the aging process advances. The most common sites for OA include the base of the thumb joint, the knees, and the hands.

The first and mildest form causes bony enlargement of the finger joints. The end joints of the fingers become bony (this is due to osteophyte formation, or reactive bone at the joint surfaces) and the hand begins to assume the appearance we associate with old age – i.e., a swollen joint involving the fingers. The base of the thumb may become swollen with bony enlargement and is the most frequently encountered site of OA.

The second form involves the spine (neck and mid- and low-back regions). Bony growths (osteophytes) appear on the spine in the neck region or in the lower back. Usually the bony growths are associated with some narrowing of the space between the vertebrae. Similar to the long-bone cartilage joint space degeneration, the process of OA in the spine begins with a degeneration of the cartilage in the disc

spaces. These disc spaces degenerate, narrow, and lead to increased forces on the bones, with subsequent osteophyte formation.

The third form involves the weight-bearing joints, most frequently involving the knees, which are followed by the hips.
The symptoms of OA may become quite severe. Osteoarthritis of the weight-bearing joints, particularly the hip and knee, develops slowly and often (but not always) involves both sides of the body. Pain in the joint may remain fairly constant or may wax and wane for a period of years and usually is activity related. In advanced cases, walking or regular activities of daily living may become difficult or even impossible. Reactive fluid (an effusion) may accumulate in the affected joint, giving it a swollen appearance. This fluid is generated from the soft tissue in the knee known as synovium, which reacts by trying to create more lubrication to make the joint surfaces smoother. A knee may feel unsteady, stiff, or have a sensation of giving out when weight is placed on it.

Additionally, a feeling of locking or grinding may be felt in the joint. Usually, in the knee, the osteoarthritis will affect the inner half of the joint more than the outer. This may result in progressive deformity with the leg becoming bowed and may cause difficulty in walking. OA involving the outer half of the knee may cause a "knock-knee" appearance. Generally, this form and deformity of arthritis is less common, and it is more often associated with other forms of arthritis, such as rheumatoid arthritis.

What is a meniscus tear?

A meniscus tear is a common knee joint injury. This rubbery tissue acts as a shock absorber between the upper and lower leg bones. Each knee has two C-shaped menisci (plural of meniscus): a lateral meniscus at the outer side of the knee and a medial meniscus at the inner side of the knee. A meniscus tear can limit your knee function.

A meniscus tear usually occurs with a twisting or pivoting motion and often with the foot planted and the knee partially flexed (for example, when lifting or playing tennis). Other knee injuries, such as a torn ligament, can happen at the same time. As you age, your meniscus becomes worn and may tear more easily. Meniscus tears are rare in young children.

The symptoms of a meniscus tear often vary. In a typical **minor tear**, there may be pain and slight swelling at first. These symptoms usually go away in 2 to 3 weeks.

In a typical **moderate tear**, you may feel pain at the side or center of the knee, depending on where the tear is located. Often, you are still able to walk. Swelling increases gradually over 2 to 3 days and may make your knee feel stiff and limit bending. There's often sharp pain with twisting or squatting. These symptoms go away but tend to recur with minor twisting or overuse.

In **severe** tears, pieces of the torn meniscus can dislocate into the joint space. This can make the knee catch, pop, or lock. You may not be able to straighten your knee. It can also feel "wobbly" or unstable, or give way without warning. The knee may swell and become stiff right after the injury, or over 2 to 3 days.

Older people whose menisci are worn may not be able to think of a specific event that caused the tear or may recall symptoms developing after a minor incident such as rising from a squatting position. Pain and minimal swelling are often the only symptoms.

A physical examination of both knees to evaluate tenderness, range of motion, and knee stability is done and k how the injury occurred and whether you have ever had any other knee injuries. X-rays are usually done.

Meniscus tear, an injury to the cartilage that protects the knee joint, depends on several things, age, health, and activity level, and when the injury occurred. Consider the following:

- The location of the tear in the meniscus is one of the most important factors in deciding whether surgery is indicated and, if so, which procedure is best.

- If you have a minor tear at the outer edge of the meniscus, you may want to choose non-surgical treatment, because often these tears heal with rest.
    - If you have a moderate to large tear at the outer edge of the meniscus, you may want to consider surgical repair (sewing the edges together), because the zone has a good blood supply, and this kind of tear tends to heal well after surgery.
    - If you have a tear that extends from the outer zone into the iner zone, the decision is more difficult. Surgery repair for these kinds of tears has varying results.
    - If you have a tear within the inner two-thirds of the meniscus, surgical repair is usually not done because there is insufficient blood supply for healing. When these tears cause symptoms, the torn pieces are usually removed (partial meniscectomy). In rare cases, the entire meniscus is removed (total meniscectomy).

- You may be able to prevent long-term complications, such as osteoarthritis, with successful surgical repair of your tear. Although no long-term studies have proven this, health professionals believe that successful meniscus repair helps to evenly distribute the forces on the knee joint. If the knee is protected from uneven force, there is a lower risk of joint degeneration.
- The pattern of the tear can determine whether your tear can be repaired. Radial tears sometimes can be repaired, depending on where they are located. Horizontal, flap, long-standing, and degenerative tears—those caused by years of wear and tear—generally cannot be repaired.

The treatment decisions depend on when the tear occurred; the location of the tear; and your age, health status, and activity level. Treatment options include:

- Non-surgical treatment with rest, ice, compression, elevation, and physical therapy. This may include temporarily wearing a knee brace.
- Surgical repair.
- Surgical removal of the torn section (meniscectomy). In rare cases, the entire meniscus is removed.

In general, surgical repair is favored over a partial or total removal. If the meniscus can be repaired successfully, saving the injured meniscus by doing a meniscal repair—rather than a partial or total meniscectomy—reduces the occurrence of knee joint degeneration.[1] Small tears located at the outer edge of the meniscus often heal with rest. Larger tears located toward the center of the meniscus may not heal well because blood supply to that area is poor. In a young person, surgery to repair the tear may be the first choice because it may restore function. See an illustration of common meniscus tears. Your age and activity level will also determine whether surgery is a good option for you. In a young person, surgery to repair a tear may be the first choice because it has a greater chance of healing and restoring a more normal function to the knee. It is generally believed that there is a poorer potential for healing in older patients, but successful repair of tears in people older than age 50 has been reported. The most common risks of surgery include infection, a blood clot in the leg, damage to nerves or blood vessels, and the risks of anesthesia.

Your treatment choices are:

- **Non-surgical treatment** to see if your knee heals on its own, wearing a temporary knee brace, and possibly starting physical rehabilitation to keep the knee muscles strong while the knee is not bearing as much weight.

- **Surgical repair** to sew the tear together.
- **Partial meniscectomy**, which is surgery to remove the torn section.
- **Total meniscectomy**, which is surgery to remove the entire meniscus. This is generally avoided, because this option increases the risk for osteoarthritis in the knee.

The decision about whether to have meniscus surgery takes into account your personal feelings and the medical facts. Following are some general considerations about meniscus surgery.

Following are some specific considerations about meniscus surgery based on the location of the meniscus tear.

Meniscus tear and the need for surgery

Location of tear	Reasons to have surgery	Reasons to wait or to not have surgery
Tears in the red zone	The success rate of surgical repair is 90% to 95%.	Many minor meniscus tears heal on their own with rest. If symptoms persist or get worse, surgery can be done at that time.
Tears extending from red to white zone	Your orthopedist may recommend surgical repair for tears in this zone, especially for younger, active people,	The success rate of surgical repair varies. There's no conclusive evidence supporting either option.

	because successful repairs restore knee function.	
Tears in the white zone	Tears in the white zone typically do not heal well after surgical repair. If they cause pain or swelling, torn pieces typically need to be removed (partial meniscectomy) and the edges need to be shaved down to make the remaining meniscus smooth.	Removing part of your meniscus (partial meniscectomy) often reduces symptoms but may increase your risk for osteoarthritis.

My knee pain won't go away. I don't think it will clear up on its own.	Yes	No	Unsure
I think surgery will help my knee in the long run.	Yes	No	Unsure
I need to be able to exercise to maintain my health, so I want to have my knee repaired.	Yes	No	Unsure
If I have to have surgery, I would rather have it done sooner than later.	Yes	No	Unsure
I want to see if my knee can be repaired and healed for next ski season (or for some other sporting activity).	Yes	No	NA*
I won't have to worry about this expense, because my insurance should cover most of the cost of this surgery.	Yes	No	Unsure

**NA=Not applicable*

Your answers in the above worksheet are meant to give you a general idea of where you stand on this decision. You may have one overriding reason to have or not to have surgery.

Intra-Articular Basic Calcium Phosphate Crystal Deposition

An understanding of the exact relationship between intra-articular BCP crystals and joint pathology is incomplete, especially as specialized techniques are required to identify the crystals. Nonetheless, existing data support the pathogenic role of BCP crystals in articular tissue degeneration. Intra-articular BCP crystal deposition has been associated with osteoarthritis and MSS, but also acute synovitis and chronic arthritis, including erosive osteoarthritis. The prevalence of intra-articular BCP crystal deposition diseases and the frequency of BCP crystal deposition in normal joints at different ages are not known. MSS and related BCP crystal-associated destructive arthropathies are also of unknown prevalence.

The concurrence of BCP crystals and osteoarthritis is well established. Crystals of BCP are frequently found in osteoarthritic cartilage, synovium and synovial fluid. Apatite crystals are found in between 30 and 67% of synovial fluid samples from patients with knee joint osteoarthritis,[4-7] depending on the sensitivity of the techniques used. It has been suggested that many osteoarthritic joint fluids contain clusters of BCP crystals that are too small or too few in number to be identified by conventional techniques. Ample data support the role of BCP crystals in cartilage degeneration, as their presence correlates strongly with the severity of radiographic osteoarthritis, and larger joint effusions are seen in affected knee joints when compared with joint fluid from osteoarthritic knees without crystals.

Nalbant *et al* recently reported the findings on a synovial fluid analysis of 330 patients with osteoarthritis. Synovial fluids were analysed by

regular and polarized light microscopy and alizarin red S staining. BCP crystals and calcium pyrophosphate dihydrate crystals were identified in 47 and 21%, respectively, with both crystal types co-existing in 16%. The presence of either crystal type correlated with the radiological grade. BCP crystals were found in 23% at the first aspiration, but in 58% at the final aspiration (at a mean interval of 3.6 ± 1.6 years, $P < 0.05$), suggesting that BCP crystals are generated as part of the pathological process in osteoarthritis.

What injuries can cause knee pain, and what other symptoms may accompany knee pain?

Injury can affect any of the ligaments, bursae, or tendons surrounding the knee joint. Injury can also affect the ligaments, cartilage, menisci (plural for meniscus), and bones forming the joint. The complexity of the design of the knee joint and the fact that it is an active weight-bearing joint are factors in making the knee one of the most commonly injured joints.

Ligament injury

Trauma can cause injury to the ligaments on the inner portion of the knee (medial collateral ligament), the outer portion of the knee (lateral collateral ligament), or within the knee (cruciate ligaments). Injuries to these areas are noticed as immediate pain, but are sometimes difficult to localize. Usually, a collateral ligament injury is felt on the inner or outer portions of the knee. A collateral ligament injury is often associated with local tenderness over the area of the ligament involved. A cruciate ligament injury is felt deep within the knee. It is sometimes noticed with a "popping" sensation with the initial trauma. A ligament injury to the knee is usually painful at rest and may be swollen and warm. The pain is usually worsened by bending the knee, putting weight on the knee, or walking. The severity of the injury can vary from mild (minor stretching or tearing of the ligament fibers, such as a low grade sprain) to severe (complete

tear of the ligament fibers). Patients can have more than one area injured in a single traumatic event.

Ligament injuries are initially treated with ice packs and immobilization, with rest and elevation. It is generally initially recommended to avoid bearing weight on the injured joint, and crutches may be required for walking. Some patients are placed in splints or braces to immobilize the joint to decrease pain and promote healing. Arthroscopic or open surgery may be necessary to repair severe injuries.

Surgical repair of ligaments can involve suturing alone, grafting, and synthetic graft repair. These procedures can be done by either open knee surgery or arthroscopic surgery (described in the section below). The decision to perform various types of surgery depends on the level of damage to the ligaments and the activity expectations of the patient. Many repairs can now be done arthroscopically. However, certain severe injuries will require an open surgical repair. Reconstruction procedures for cruciate ligaments are increasingly successful with current surgical techniques.

Meniscus tears

The meniscus can be torn with the shearing forces of rotation that are applied to the knee during sharp, rapid motions. This is especially common in sports requiring reaction body movements. There is a higher incidence with aging and degeneration of the underlying cartilage. More than one tear can be present in an individual meniscus. The patient with a meniscal tear may have a rapid onset of a popping sensation with a certain activity or movement of the knee. Occasionally, it is associated with swelling and warmth in the knee. It is often associated with locking or an unstable sensation in the knee joint. The doctor can perform certain maneuvers while examining the knee which might provide further clues to the presence of a meniscal tear.

Routine x-rays, while they do not reveal a meniscal tear, can be used to exclude other problems of the knee joint. The meniscal tear can be diagnosed in one of three ways: arthroscopy, arthrography, or an MRI. Arthroscopy is a surgical technique by which a small diameter video camera is inserted through tiny incisions on the sides of the knee for the purposes of examining and repairing internal knee joint problems. Tiny instruments can be used during arthroscopy to repair the torn meniscus.

Arthrography is a radiology technique whereby a contrast liquid is directly injected into the knee joint and internal structures of the knee joint thereby become visible on x-ray film. An MRI scan is another radiology technique whereby magnetic fields and a computer combine to produce two- or three-dimensional images of the internal structures of the body. It does not use x-rays, and can give accurate information about the internal structures of the knee when considering a surgical intervention. Meniscal tears are often visible using an MRI scanner. MRI scans have largely replaced arthrography in diagnosing meniscal tears of the knee. Meniscal tears are generally repaired arthroscopically.

Tendinitis

Tendinitis of the knee occurs in the front of the knee below the kneecap at the patellar tendon (patellar tendinitis) or in the back of the knee at the popliteal tendon (popliteal tendinitis). Tendinitis is an inflammation of the tendon, which is often produced by a strain event, such as jumping. Patellar tendinitis, therefore, also has the name "jumper's knee." Tendinitis is diagnosed based on the presence of pain and tenderness localized to the tendon. It is treated with a combination of ice packs, immobilization with a knee brace as needed, rest, and anti-inflammatory medications. Gradually, exercise programs can rehabilitate the tissues in and around the involved tendon. Cortisone injections, which can be given for tendinitis elsewhere, are generally avoided in patellar tendinitis because there are reports of risk of tendon rupture as a result of corticosteroids in

this area. In severe cases, surgery can be required. A rupture of the tendon below or above the kneecap can occur. When it does, there may be bleeding within the knee joint and extreme pain with any knee movement. Surgical repair of the ruptured tendon is often necessary.

Fractures

With severe knee trauma, such as motor vehicle accidents and impact traumas, bone breakage (fracture) of any of the three bones of the knee can occur. Bone fractures within the knee joint can be serious and can require surgical repair as well as immobilization with casting or other supports.

Causes and Risk Factors of Degenerative Joint Disease

Osteoarthritis is the most common form of joint disease, sparing no age, race, or geographic area. Symptomatic disease increases with age. Many patients may have OA seen on x-rays, but not be overly symptomatic.

Hereditary, injury, fractures around a joint surface, and overuse factors are most frequently involved in the development of osteoarthritis. Osteoarthritis may occur secondary to an injury to the joint due to a fracture, repetitive or overuse injury, or metabolic disorders (e.g., hyperparathyroidism). Additionally, gout and other forms of crystalline joint disease may lead to OA of a joint. Obesity or being overweight is a risk factor for knee osteoarthritis more commonly in females; this is less commonly seen in the hip joint. Recreational running does not increase the incidence of OA, but participation in competitive contact sports does. Specifically, impact sports that repetitively load a joint increase the injury to a joint. If cartilage in a joint is injured, it cannot regenerate, and the new forces that are created are abnormal, leading to further stresses, and the cycle may propagate.

Symptoms of Degenerative Joint Disease

Initially there may be joint stiffness, usually lasting more than 15 minutes, and typically following activity of the joint. Later there may be pain on motion of the affected joint, which is made worse with activity or weight-bearing and relieved by rest. Typically OA improves with rest and does not remain symptomatic at night time. It is usually better in the morning, and it worsens as the day progresses.

There may be limitation of motion of the affected joint, although this is a later finding. Coarse crepitus (a creaking or cracking) may be felt in the joint. There is usually some mild joint swelling and tenderness to touch. The joint may feel warm. A joint that cracks and snaps does not necessarily mean arthritis is present and many patients are able to make their joints crack without having pain.

Diagnosis of Degenerative Joint Disease

Diagnosis is based on the medical history, physical examination, and x-ray findings. Lab tests do reveal signs of inflammation, but must be performed to rule out other arthritic disorders.

Treatment of Degenerative Joint Disease

Treatment of OA depends upon multiple factors including patient age, activities, medical condition, and x-ray findings. Patients with mild to moderate osteoarthritis of weight-bearing joints (hips and knees) may benefit from a supervised exercise program such as walking. Non-impact activities such as swimming, cycling, and walking tend to be more comfortable for patients with OA. In a younger patient with signs or symptoms of OA, other causes of arthritis such as deformity, medical conditions, or bone disorders should be carefully sought for in order to rule out other conditions.

A program of regular physical activity can strengthen the muscles, tendons, and ligaments surrounding the affected joints and preserve mobility in joints that are developing bone spurs. Many physicians believe that osteoarthritis may be prevented by good health habits.

Remaining active, maintaining an ideal body weight, and exercising the muscles and joints regularly helps to nourish cartilage.

A first line of simple treatment - acetaminophen (Tylenol) is as effective and has fewer side effects than other non-steroidal anti-inflammatory drugs (NSAIDS) such as ibuprofen, naproxen, or aspirin.

Glucosamine-chondroitin sulfate may be prescribed by your doctor. This medication, when taken over a period of months, may reduce pain and symptoms by restoring or replenishing nutrition to diseased cartilage cells. It tends to be more effective in earlier stages of OA. The dosage and combination of each ingredient is an important aspect of the therapy, as not all preparations and brands are the same. Patients who fail to improve on acetaminophen or glucosamine may be treated with salicylates and other oral anti-inflammatories. Previously, medications such as Vioxx, Celebrex, and Bextra (Cox-2 NSAIDS) were preferred due to less gastrointestinal side effects (ulcers) and improved pain relief for arthritis. However, currently the use of these medications should be reviewed with your doctor, as concerns about their use in certain patients have been recently reported. More traditional NSAIDS (ibuprofen, naproxen, etc.) are available over the counter, and they also provide excellent relief of symptoms. Capsaicin cream 0.25% applied twice daily may reduce knee pain. Intra-articular (within the joint) injections of steroids may also be helpful, although the duration and amount of pain relief is often unpredictable, especially in more advanced stages of OA. Alternative injections of hyaluronic acid preparations (sodium hyaluronate) are also available and may be very useful in the treatment of OA. These injections are indicated for OA of the knee, and typically require an injection once a week, over a period of three to five weeks (i.e., three to five injections). The hyaluronic acid is injected into the knee joint, and similar to oral glucosamine, may provide nutrition to the diseased cartilage cells and collagen within the cartilage. The fluid is a gel-like material that appears to act initially like a lubricant for the joint. However, studies have shown that the

lubricant aspect plays little role and, in fact, the fluid is absorbed quickly by the cartilage cells.

Bracing, splinting, and other orthotic treatments may be useful in managing or "unloading" an arthritic joint surface. These non-operative treatments are simple, often effective, however cost and ease of use are factors in their selection in treatment.

Surgery may be dramatically effective for patients with severe osteoarthritis of the weight-bearing joints. Total hip replacement and newer hip resurfacing replacements and total knee replacement or unicompartmental (partial) knee replacement can be extremely effective. Joint replacement is now being performed in younger patients also. The concerns about wear of the prosthetic joint surface in younger patients make this the most challenging aspect of future research in this area. Newer joint surfaces for joint replacement including highly cross-linked polyethylene, metal on metal bearing, ceramic bearings, and others have emerged and currently are available in the U.S.

Although arthroscopic surgery for knee osteoarthritis is a common procedure, its long-term effectiveness is unclear, and may be best for symptoms such as catching, locking, or those that have been present for only a short duration. In addition, not all patients that have arthritis should have an arthroscopy, as this may not improve their symptoms.

In younger patients, hip and knee preserving procedures should be considered, in order to avoid a hip or knee replacement. Although performed less frequently, hip and knee preserving procedures, such as osteotomy (cutting the bone and realigning the bone or joint surface), may restore a joint to a normal alignment and be an excellent alternative to joint replacement.

Alternative Degenerative Joint Disease

Experimental techniques to repair cartilage loss in the knee by transplantation of cartilage cells are promising. This is most effective in small, localized areas of cartilage loss and not in advanced arthritis. These procedures also may be combined with joint osteotomy to alter joint alignment in order to allow this new cartilage to heal.

Prevention of Degenerative Joint Disease

Weight reduction may reduce the risk of symptomatic knee osteoarthritis and, more importantly, reduce the symptoms of OA in the knee in overweigh patients.

If you have an injury to your joint, activity modification while maintaining an active lifestyle and joint range of motion provide for a healthy joint recovery.

Clinical Highlights and Recommendations:

- Schedule a same-day appointment if a patient reports the following: hot, swollen joint with or without fever and/or feeling ill, cannot bear weight on leg, leg or foot is cool or blue, deformity, severe pain, locked knee, and/or patient demands to be seen the same day.
- For patients who are not scheduled for a same-day visit, provide advice on basic techniques to reduce pain and inflammation in the knee. These include rest, ice, compression, elevation, and the use of appropriate over-the-counter analgesics.
- When a patient is diagnosed with degenerative joint disease of the knee, avoid obtaining an x-ray on the first visit unless specifically indicated.
- Educate the patient regarding overall goals of treatment. These include education regarding the disease and self-management, pain reduction, exercise that promotes joint health, and improvement in patient functioning and safety. Consider referral to physical therapy.

Priority Aims:

1. Improve the efficacy of diagnostic imaging for evaluating degenerative joint disease.
2. Increase the use of recommended conservative approach as first-line treatment for degenerative joint disease.
3. Increase patient education for patients with degenerative joint disease.

Additional Background:

DJD is a heterogenous class of joint disorders characterized by degeneration and loss of cartilage, alteration of subchondral bone, and associated soft tissue changes that may be due to a variety of causes. These changes, which are the result of cartilage injury exceeding the rate of cartilage repair, occur gradually over time. Clinical criteria for the definitive diagnosis of degenerative joint disease of the knee are based on history, physical examination, and roentgenologic findings that may occur late after the onset of pathologic findings. Degenerative joint disease, for the purposes of this guideline, includes patients, in whom cartilage injury may exceed the rate of repair, resulting in the potential for progressive joint destruction.

What are diseases and conditions that can cause knee pain, and how are they treated?

Pain can occur in the knee from diseases or conditions that involve the knee joint, the soft tissues and bones surrounding the knee, or the nerves that supply sensation to the knee area. In fact, the knee joint is the most commonly involved joint in rheumatic diseases, immune diseases that affect various tissues of the body including the joints to cause arthritis.

Arthritis is inflammation within a joint. The causes of knee joint inflammation range from non-inflammatory types of arthritis such as osteoarthritis, which is a degeneration of the cartilage of the knee, to inflammatory types of arthritis (such as rheumatoid arthritis or gout). Treatment of the arthritis is directed according to the nature of the specific type of arthritis.

Swelling of the knee joint from arthritis can lead to a localized collection of fluid accumulating in a cyst behind the knee. This is referred to as a Baker cyst and is a common cause of pain at the back of the knee.

Infections of the bone or joint can rarely be a serious cause of knee pain and have associated signs of infection including fever, extreme heat, warmth of the joint, chills of the body, and may be associated with puncture wounds in the area around the knee.

Tumors involving the joint are extremely rare. They can cause problems with local pain.

The collateral ligament on the inside of the knee joint can become calcified and is referred to as Pellegrini-Stieda syndrome. With this condition, the knee can become inflamed and can be treated conservatively with ice packs, immobilization, and rest. Infrequently, it requires a local injection of corticosteroids.

Chondromalacia refers to a softening of the cartilage under the kneecap (patella). It is a common cause of deep knee pain and stiffness in younger women and can be associated with pain and stiffness after prolonged sitting and climbing stairs or hills. While treatment with anti-inflammatory medications, ice packs, and rest can help, long-term relief is best achieved by strengthening exercises for the quadriceps muscles of the front of the thigh.

Bursitis of the knee commonly occurs on the inside of the knee (anserine bursitis) and the front of the kneecap (patellar bursitis, or "housemaid's knee"). Bursitis is generally treated with ice packs,

immobilization, and anti-inflammatory medications such as ibuprofen (Advil, Motrin) or aspirin and may require local injections of corticosteroids (cortisone medication) as well as exercise therapy to develop the musculature of the front of the thigh.

Knee pain at a glance

> The knee joint has three compartments.
> Causes of knee pain include injury, degeneration, arthritis, infrequently infection, and rarely bone tumors.
> Ligaments within the knee (cruciate ligaments) and on the inner and outer sides of the knee (collateral ligaments) stabilize the joint.
> Surgical repair of ligament injury can involve suturing, grafting, and synthetic graft repair.
> Routine x-rays do not reveal meniscus tears, but can be used to exclude other problems of the bones and other tissues.

The knee joint is the most commonly involved joint in rheumatic diseases, immune diseases that affect various tissues of the body including the joints to cause arthritis.

Osteoarthris of the Knee

> Osteoarthritis, sometimes called degenerative arthritis, is caused by breakdown of the articular cartilage on the ends of the bones inside the joints. When the cartilage wears totally off the end of the bones, there is bone-on-bone contact. This is usually rather painful.
>
> Articular cartilage is the slick white substance that covers the end of the bones and joints and is abnormal or worn in patients with arthritis. If you take a chicken joint and pull it apart, there is a glistening white substance on the ends of the bone. This is an example of articular cartilage.

The cause of osteoarthritis is not completely known. Exactly why the articular cartilage begins to breakdown and the normally sliding surfaces become pitted and irregular is not known, but it is felt to be degenerative in nature and occurs along with degeneration of other body tissues, which is all part of the ageing process. Nearly 90% of all people over the age of sixty years show some signs of osteoarthritis.

Injury to the joint can be a cause.

Arthritis does not only affect the knee joint, it affects most joints in the body. The knee and hip are two of the most significantly and frequently involved joints.

Do not confuse osteoarthritis with rheumatoid arthritis or any of the other inflammatory types of arthritis such as lupus, ankylosing spondylitis and other diseases which attack the lining of the knee joint, which subsequently attacks the joint surfaces. The symptoms of osteoarthritis vary greatly. For many people, it is only a minor temporary nuisance which can be relieved with medication. For others, it can be a very uncomfortable and painful existence.

Activities of daily living and even sleeping can be difficult. Some people have more severe symptoms than others and in fact, x-rays alone are not a good indicator of how much the patient is suffering. There is therefore, great variation in the amount of discomfort experienced in individuals. Because there are over one hundred different types of arthritis, sometimes a complete medical evaluation is needed. Osteoarthritis is by far the most common type of arthritis and can usually be diagnosed from your symptoms, physical examination, joint involvement and x-rays. The articular cartilage cannot be seen directly but its breakdown shows up on x-rays as a narrowing of the gap between the bones. Also, with degenerative arthritic changes, there can be increased deposition of bone about the joint which will show up as spurs.

Sometimes bone can be reabsorbed and this will show up as degenerative cysts. Both spurs and cysts can be frequently seen on x-rays around the joint. These spurs and cysts are benign and are related to the degenerative process.

Occasionally, blood tests are necessary to be sure those other types of arthritis, such as rheumatoid arthritis and gout are not present. In addition, if you have an excess amount of fluid in the knee joint, some of your joint fluid may need to be drawn off and this can be sent for evaluation under the microscope as well as for chemical analysis of the fluid, which can help differentiate osteoarthritis from other types of arthritis.

Treatment goals have to be individualised for each patient. Osteoarthritis cannot be cured and the degenerative process cannot be stopped. However, a balanced treatment program can reduce pain and improve joint function. This allows the patient to live a more active and pleasurable life. In recent years, new medications have been made available for the treatment of pain and inflammation of osteoarthritis. All of them have a similar chemical make up and can cause irritation to the stomach. Your symptoms and the start of your arthritic process will influence the type of anti-inflammatory medication that will be recommend for you. Some people are unable to tolerate some of the anti-inflammatories because of side effects, but can take others without much difficulty. A different non-steroidal anti-inflammatory medication may work well for some but not work for you. The proper medication should be prescribed for you and tailored to your particular condition. Physiotherapy is also important in the treatment of arthritis. By strengthening the muscles around the knee, you can improve the general "health" of your knee.
In addition, it is very important to maintain an appropriate body weight. Certainly, being overweight places significant stress on your joints. Keeping your weight at an acceptable level frequently makes the symptoms much less marked and in addition, can potentially avoid the possibility of surgery. If pain or discomfort

persists despite an appropriate conservative treatment program, surgery may be helpful.

There are several different operative procedures which may be performed for osteoarthritis. The first alternative is arthroscopic joint debridement and shaving of the roughened joint surfaces, as well as dealing with possible degenerative cartilage tears in the knee at the same time. This operative procedure can be performed in those patients who do not have markedly advanced degenerative changes present. For the ones with more advanced degenerative changes present, larger surgical procedures will be necessary. In younger individuals who have arthritis predominantly only on one side of the knee joint, an operation known as an osteotomy can be performed. This is where the leg bone is cut and realigned to allow transmission of forces across the good side of the knee. If the arthritis involves the entirety of the knee joint, an osteotomy would not be successful. The only other alternative in an older patient would be a total knee replacement. With the development of synthetic materials, total joint replacement surgery has become a practical solution to advanced osteoarthritis. Total knee replacements are very successful; however they do involve major surgery.

Another type of surgery is a "uni-compartmental arthroplasty". This involves replacing the side of the joint that is arthritic. It is less traumatic than a total knee replacement, and has an easier recovery, but they are not suitable for most people.

Do not expect a new joint to perform as well as the one Mother Nature provided. Total knee replacement involves retreading the joint surface with metal and plastic implants. This is done as a last resort in the treatment of your knee condition when all conservative methods have failed. This operation is done primarily to relieve pain and discomfort and improve function. The results have been gratifying, although there are some significant

complications which can occur in a relatively small percentage of patients.

The goal with osteoarthritis is to treat each patient individually, consisting initially of conservative treatment and if that fails, proceed with surgery selectively tailored to each individual's situation.

In summary, many people with osteoarthritis lead normal and active lives. Medication and physiotherapy can help reduce pain and restore movement to stiff joints. If necessary, surgery can be used to improve function of the joints, decrease pain and discomfort and improve the quality of life. Although osteoarthritis cannot be cured its symptoms can be managed and the patient can often enjoy a more useful and active lifestyle.

New Insights into Degeneration of Knee Joints

Medical researchers believe that exercise and other mechanical stresses help renew tissue in the knee - but that coupled with an immune system response, could lead to osteoarthritis in the knee.

While the mechanical stresses of normal exercise are important for the health of the meniscus '“ a layer of buffering tissue in the knee joint '“ these stresses coupled with a potent immune system response can lead to the ultimate degeneration of the knee joint as seen in osteoarthritis.

Furthermore, the chemical nitric oxide is a critical "signal" in controlling how the immune system responds to the stress. This insight could lead to new therapies for osteoarthritis that would target this interaction between nitric oxide and the inflammatory response.

The primary function of the meniscus -- which is located within the knee joint between the thigh bone (tibia) and the lower leg bone (femur) -- is to act as a shock absorber and a distributor of weight

within the joint. It is a type of cartilage made up of a matrix of fibers, primarily collagen, which provide toughness and durability.

"Contrary to common perception, the meniscus is a living tissue that is slowly and continually breaking down old collagen and building new collagen," according to the Journal of Applied Physiology. "We have found that mechanical stresses on the meniscus '“such as what would be expected in normal exercise -- can be beneficial to this process, however, even slight imbalances can negatively affect this process. Studies have shown that inflammation can cause the meniscus to lose its ability to build new matrix."

In their experiments, researchers took samples of meniscus tissue from pigs, and in a controlled fashion subjected the samples to various pressures under different conditions. In the first experiment, they compared the samples that reacted to mechanical stress with those that did not. The samples that underwent compression showed a significant increase in the production of key building blocks of the meniscus. Specifically, protein synthesis increased 68 percent, while proteoglycan, the substance that gives the meniscus its ability to absorb shocks, increased by 58 percent. It has been postulated that interleukin-1 (IL-1), one of a family of pro-inflammatory proteins secreted by potent immune system cells, plays a role in the destruction of cartilage as seen in osteoarthritis. So the researchers then performed the compression experiments in the presence of IL-1.

"We found that the stimulatory effect of the mechanical stress was prevented by the presence of IL-1," Guilak said. "This finding suggests that an inflammatory environment may alter the physiological response of the meniscus to mechanical stress."

Interestingly, however, the researchers also found that if they inhibited the synthesis of nitric oxide, the beneficial effects of mechanical stress returned, even in the presence of IL-1. Nitric oxide is a free-radical which in elevated amounts can be toxic to tissues. In normal concentrations, it helps in resistance to infections and in blood vessel dilation. Furthermore, when the researchers inhibited

nitric oxide, they found a significant reduction in the breakdown of the meniscus caused by inflammation.

"Although the mechanisms of the interaction between IL-1 and nitric oxide are not well understood, it would appear that the negative impact on of IL-1 on the rebuilding of the meniscus is mediated by nitric oxide," Guilak said. "It appears clear that both inflammation and mechanical stress are important factors in matrix turnover in the meniscus.

"No one has really looked this closely at the meniscus because it was thought that it was not important to the joint," Guilak continued. "Not long ago, if the meniscus was damaged, surgeons just removed it. However, within five to 10 years, patients would develop osteoarthritis. Now, surgeons are doing whatever they can to preserve the meniscus."

A new research effort aimed at better understanding the role of obesity and exercise in osteoarthritis. While the benefits of exercise seem apparent, researchers are beginning to see obesity as a low-grade systemic inflammatory disease, since the obese tend to have elevated levels of numerous markers of inflammation. This, Guilak said, offers the potential for developing ways to prevent or forestall the joint destruction seen in osteoarthritis.

Two health claim petitions were submitted to FDA. One petition was submitted on behalf of Weider Nutrition International, Inc. (petitioner A) and the other was submitted on behalf of Rotta Pharmaceutical, Inc. (petitioner B). The claims concerned the relationships between the consumption of: (1) glucosamine and/or chondroitin sulfate and reduction in the risk of: osteoarthritis; joint degeneration; and cartilage deterioration (petitioner A), and; (2) crystalline glucosamine sulfate and a reduced risk of osteoarthritis (petitioner B). The following is a brief synopsis of the scientific data provided in the petitions, and the conclusions reached by the petitioners. This synopsis is of the petitions alone and does not include any FDA conclusions. .

I. Synopsis of Petitions (Note: Letters "A" and "B" preceding reference numbers correspond to the citations from petitioner A (Weider Nutrition International, Inc.) and petitioner B (Rotta Pharmaceutical, Inc.), respectively.)

A. Substance

Glucosamine is a glycoprotein derived from marine exoskeletons or produced synthetically. It is sold as the sulfate sodium chloride (sulfate) salt, hydrochloride (HCL) salt and N-acetyl-glucosamine. It is an endogenous substance that is required for the synthesis of glycoproteins, glycolipids, and glycosaminoglycans (also known as mucopolysaccharides). These carbohydrate- containing compounds are found in tendons, ligaments, cartilage, synovial fluid, mucous membranes, and structures in the eye, blood vessels, and heart valves.

Chondroitin sulfate belongs to a class of very large molecules called glucosaminoglycans (GAGs), which is made up of glucuronic acid and galactosamine. Chondroitin is manufactured from natural sources, such as shark and bovine cartilage. Pure chondroitin is a relatively large molecule, weighing about 16,900 daltons. The species or tissue of origin, and the extraction method used, can affect the size of the molecule.

B. In vitro mechanistic data

Studies in human and animal primary cell cultures, established cell culture models, and tissue/organ cultures have reported various biochemical effects following exposure to glucosamine sulfate, glucosamine hydrochloride (HCl), and chondroitin sulfate. Preliminary research suggests that glucosamine affects cytokine-mediated pathways regulating inflammation and cartilage degradation and immune responses. Glucosamine seems to inhibit interleukin 1-beta (IL-1□□, thereby reducing inflammation and cartilage degradation Glucosamine reportedly stimulated proteoglycan synthesis, which may also be through inhibition of IL-1. In addition, glucosamine reportedly possesses immunomodulatory activity and

has been reported to be a substrate for and stimulate new chondroitin sulfate synthesis.

Chondroitin sulfate has been reported to stimulate production of proteoglycans and prevent cartilage degradation , possibly via inhibition of IL-1. Reports also suggest a role for chondroitin sulfate in prevention of inflammation and immunomodulation.

C. Animal models of OA

Dietary glucosamine sulfate has been reported to reduce kaolin- and adjuvant-induced tibio-tarsal arthritis in rats and glucosamine-HCL, with and without chondroitin sulfate, was reported to reduce cartilage degredation in a rabbit model of OA. Consumption of glucosamine-HCl has been reported to enhance the rate of new articular cartilage proteoglycan synthesis in mice. Diets supplemented with chondroitin sulfates have been reported to prevent articular cartilage degredation induced by chymopapin in rabbits, Freund's adjuvant in mice (A163) and in a rabbit surgical instability model of OA.

D. Human clinical studies

1. Mitigation of Symptoms

Relief of OA symptoms has been reported in OA patients taking glucosamine hydrochloride, glucosamine sulfate, chondroitin sulfate, and combination products of glucosamine plus chondroitin sulfate. The majority of the studies are on glucosamine sulfate relieving the symptoms of knee OA. Studies lasting from a few weeks to three years have reported that oral glucosamine sulfate/hydrochloride, chondroitin sulfate and their combination products can significantly improve symptoms of pain and functionality indices in patients with osteoarthritis. Relief of OA symptoms by glucosamine and chondroitin sulfate has been compared with the non-steroidal anti-inflammatory drugs (NSAIDs) ibuprofen, diclofenac sulfate and naproxen.

2. Joint Degeneration and Cartilage Deterioration
Radiographic evidence suggests that glucosamine sulfate and chondroitin sulfate may slow joint degeneration in patients with osteoarthritis. OA patients taking glucosamine sulfate for up to three years had significantly less knee joint degeneration, less joint space narrowing, and significant symptom improvement when compared with placebo Progression of knee joint space narrowing was reportedly prevented in OA patients taking chondroitin sulfate for one to three years when compared with placebo or baseline..

Compared with placebo, consumption of chondroitin sulfate for three years did not prevent development of OA in finger joints that were non-affected at the start of the study, but a significant decrease in the number of patients with new "erosive" OA finger joints was reportedly observed . In a separate two year study, chondroitin sulfate plus naproxen did not prevent development of OA in finger joints that were non-affected at the start of the study, but compared with naproxen alone, a significant decrease in the number of joints with new erosions was reportedly observed .

Investigators have reported biochemical evidence from OA patients that chondroitin sulfate may protect against cartilage and bone degradation. Compared with placebo, one year treatment of OA patients with chondroitin sulfate was reported **to decrease markers of bone metabolism (serum osteocalcin, urine pyridinoline/deoxypyridinoline) and cartilage metabolism (serum keratin sulfate, cartilage oligometric matrix protein. Compared with pre-treatment levels, short term treatment (5-10 days) with chondroitin sulfate elevated synovial fluid proteoglycan and hyaluronic acid levels and decreased collagenolytic activity, phospholipase A2 and N-acetylglucosaminidase**.

II. Petitioners' Conclusions

A. Petitioner A (Weider Nutrition International, Inc.)

The following conclusions are found on page 23 of petitioner's Exhibit 1 (scientific summary) submitted by petitioner A.

1. Maintaining the structural and functional integrity of the proteoglycan component of the extracellular matrix of articular cartilage is required for preservation of healthy joint architecture and biomechanics.
2. Imbalanced metabolism favoring catabolism within the extracellular matrix of articular cartilage produces degenerative changes in the proteoglycan composition of the matrix.
3. Compromise of the structural and functional integrity of the proteoglycan component of the extracellular matrix of articular cartilage results in net loss of articular cartilage tissue, inferior biomechanical competence and structural deformation of joint architecture.
4. Net degradation of the extracellular matrix of articular cartilage, accompanied by the production of spontaneous repair matrix with abnormal proteoglycan composition, results in asymptomatic subclinical osteoarthritic change.
5. The progression of degenerative asymptomatic osteoarthritic change to osteoarthritis is not inevitable.
6. The progression of degenerative osteoarthritic change is required in order for abnormalities in articular cartilage composition and structure to progress to osteoarthritis.
7. Osteoarthritic change in the absence of joint pain represents a modifiable risk factor for later development of osteoarthritis.
8. Dietary supplementation with D-glucosamine, glucosamine-HCL, glucosamine sulfate or chondroitin sulfate contributes to the preservation of articular cartilage, inhibits the initiation of osteoarthritic change in articular cartilage and inhibits the progression of osteoarthritic change to symptomatic osteoarthritis.
9. Dietary supplementation with D-glucosamine, glucosamine-HCL, glucosamine sulfate or chondroitin sulfate is an effective

> modifier of osteoarthritic change and reduces the risk for osteoarthritis.

B. Petitioner B (Rotta Pharmaceutical, Inc.).
The following conclusions are found on pages 5 and 45 of the petition.

> "The scientific evidence in this Petition convincingly establishes that crystalline glucosamine sulfate, when given to individuals diagnosed with osteoarthritis, can prevent further joint degradation, can reverse the symptoms by minimizing the inflammation and restoring articular cartilage, can reduce joint pain and can result in increased joint function. Given the physiological mechanism of action of crystalline glucosamine sulfate and other factors, there also are sufficient data demonstrating the ability of crystalline glucosamine sulfate to be effective in reducing the risk of developing osteoarthritis."

"The preventative effects of crystalline glucosamine sulfate in this patient population with "mild osteoarthritis," a patient population very similar to the "healthy population," combined with the well-known mechanism of action for crystalline glucosamine sulfate support the ability of crystalline glucosamine sulfate to be effective in preventing the onset of osteoarthritis."