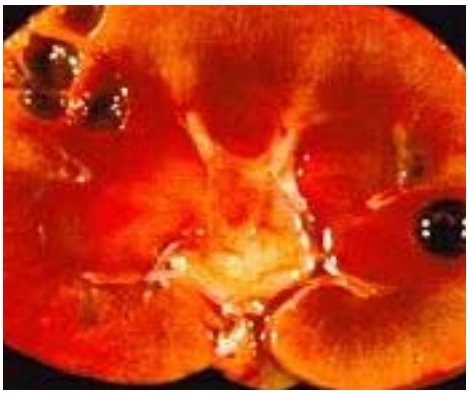
THE CAT FANCIERS' ASSOCIATION



HERITABLE DISEASES AND ABNORMALITIES IN CATS

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Genetic diseases and/or abnormalities are a fact of everyone's life, humans as well as cats. All of us have some genes that function improperly or not at all. These genes may or may not be seen in our physical bodies, but they are present and when we produce offspring, the resultant individual has genes that are a mixture of ourselves and our mate. Genes give us the ability to be taller or shorter, with blue eyes or brown and hair that is black or brown or blonde. They also affect our blood type and whether we are at risk for a variety of diseases. (For more information, see the section called Basic Genetics for Cat Breeders, elsewhere on this CD).

In cats, the same situation occurs. Scientists tell us that any cat can have at least 5 genes that are not functional or may be malfunctioning just by random chance. With our pedigreed animals, we have increased the chances that such abnormalities or diseases can occur through selective breeding that leads to cats that are more alike in resultant generations. Along with the good genes come a few that may not be considered desirable.

Scientists classify these diseases and abnormalities into categories:

1. Inborn errors of metabolism
2. Congenital abnormalities
3. Structural abnormalities
4. Other

With the advent of new technologies that are able to "see" into the genetic makeup of cells or chromosomes, the Human Genome Project began in the 1980's. Scientists have been working on feline genetics for decades and a more focused feline genome project has been in progress since the early 1990's.The development of genetic tools and resources have now advanced to a stage that scientists can proceed more rapidly and efficiently to identify which genes control which diseases or abnormal traits. Some are easy because they are a simple dominant or recessive and easy to identify. Others are not because they are caused by more than one gene or are a combination of genes and environmental factors.

With each passing year, more is being learned about feline genetic diseases and defects. Research methods are advancing rapidly and the advent of DNA-based technologies has opened up new avenues for genetic research in cats. The cat also serves as the model for many human genetic diseases, and both species have benefited greatly from research into these problems. The list of anomalies or diseases presented here tabulates the major, currently identified feline diseases or abnormalities known or suspected to have a genetic component as well as some common issues which we see in cats. It is not an all inclusive list, but can give us a good idea of the variety and severity of each. No doubt as time goes by, the list will become longer. While the cat breeds most associated with each condition are noted because this is where the trait or issue has been identified and literature exists to discuss the issue, almost all of these diseases and defects can be found in other pedigreed varieties and are also found in the domestic, non-pedigreed population.

One of the issues that plagues breeders is that an article appears in print discussing a particular abnormality or disease, and the breed is labeled as having that problem by veterinarians. I can remember a veterinarian in the 1980's telling me that all Abyssinians have cardiomyopathy when in fact, it was found a year later that the deficiency in taurine in cat foods caused the cardiomyopathy in my breeding stock as well as everyone else's and in non-pedigreed populations as well. I went back to this veterinarian and asked him to retract his statements and written documents, since the breeders who brought him examples of this problem were only acting as his "early warning system" for a widespread problem.

Thus, it is important for veterinarians and for breeders to work together to determine just what the abnormality is and what caused it rather than jumping to conclusions about a breed without enough information to make a determination. It is also important to understand the difference between the terms "congenital" and "inherited". Congenital defects are those seen in newborns or the very young. They may or may not be inherited. An example of a non-inherited congenital defect is the occurrence of cleft palates in kittens born to queens given the drug griseofulvin during pregnancy. Inherited defects may or may not be present at birth. In many cases, they do not become evident until later in life.

John Armstrong, in his article "The Nature of Genetic Disease", describes what he believes to be the first clear description of the relationship between genotype and metabolic disorders:

> *The first clearly-described relationship between genotype and metabolic deficiencies is credited to Sir Archibald Garrod, an English physician. In 1901, he showed that the inherited disease alkaptonuria results from an inability to metabolize certain amino acids, leading to the accumulation of homogentisic acid. Some of this compound accumulates in skin and cartilage (the latter leading to arthritis). The rest is excreted in the urine, turning it black. Garrod suggested that the metabolic block was caused by an enzyme deficiency, though this was not confirmed until the enzyme (homogentisic acid oxidase) was characterized in 1958.*

So what does this mean? Since Garrod's time, many other inherited metabolic diseases have been discovered. Some can be managed by careful attention to diet; others cannot. Certainly, cats with these metabolic diseases are not good candidates for a breeding program. A particularly nasty example is Tay-Sachs disease in humans, which involves an enzyme important in lipid metabolism. Individuals who have two alleles (homozygous) for a deficiency in this enzyme accumulate a compound called a ganglioside in the nervous system. They appear normal at birth but progressively lose motor functions and die around 3 years of age. At this time, there is no treatment.

Most of these inborn error conditions in cats also involve mutations that lead to the production of a nonfunctional enzyme, or one that is totally absent. In heterozygotes, the single good copy of the gene is generally able to produce sufficient enzyme to handle the normal workload. However, in a few cases, carriers as well as affected individuals have to be careful about their diet, or may exhibit less severe phenotypic effects.

The importance for breeders is clearly evident: if one of these deficiencies is found in one of your kittens, you do not want to perpetuate it in your breeding program – no matter how pretty the cat is or how successful it might be in the show ring. I call these cats the real heartbreakers, because, although they may be lovely to look at, they could perpetuate the problem for generations to come. The recommendation from veterinarians, researchers, and ethicists is to neuter or spay the animal and go on.

There are laboratories that have established diagnostic tests that allow a specific diagnosis of a genetic error of metabolism or other heritable disease. Inborn errors of metabolism include all biochemical disorders due to a genetically determined, specific defect in the structure and/or function of a protein molecule. These may include enzyme deficiencies, genetic defects in structural protein receptors, plasma and membrane transport proteins, or other proteins necessary for normal biological function. Chemistry tests of blood or urine can identify the metabolic pathway that is defective. Once the defective protein is identified, the search for the causative gene mutation is begun. When the mutation is found, DNA testing will replace chemistry testing for this disease, as it is more accurate. DNA is very stable and only a very small amount is needed. Swabs from the inside lip/cheek of a cat are easily obtained with a cytology brush and provide enough sample for multiple tests. These swabs, once completely air dried, can be mailed with no special handling and can keep for years it protected from excessive moisture and bacterial contamination.

Once the sample is collected, the DNA segment of interest is amplified with appropriate primers and a procedure called polymerase chain reaction (PCR). The mutant and/or normal allele are identified by DNA size difference directly on a gel in case of deletions or insertions that change the size of the DNA fragment or after enzymes have specifically cut the DNA into fragments for mutations that change a single nucleotide. A DNA test will identify whether a cat is homozygous for the normal allele, heterozygous for the mutation (a “carrier” of a recessive disease), or homozygous for the mutation.

KNOWN FELINE GENETIC DISEASES AND ABNORMALITIES:

The diseases and abnormalities described below have been reported in cats. Some are more common than others. When literature reports are in print, they have been mentioned here. If, as a breeder, you come across these abnormalities, the affected animals are not good candidates for breeding programs.

ABDOMINAL (umbilical) HERNIAS: When kittens are born, sometimes a hernia (tear) develops at the site of the umbilicus and the intestine protrudes through this tear. This tear can be repaired surgically and is easily done by your veterinarian. However, if your breeding stock continues to have these hernias, then this is a genetic issue, with weakness in this area of the belly. It is important to make an effort to select breeding stock that does not carry or produce this trait. It is, however, a random trait that is developmental and abnormal.

ABNORMAL HIPS IN FEMALES: If there is a female in a breeding program that always needs a Caesarian section to deliver a litter because the hip structure is not large enough to accommodate the descension of kittens down the birth canal, she is not a desirable breeding female, no matter how pretty she is. An offspring can be kept and mated instead. If that offspring continues with the same problem, the trait is better off being eliminated from your breeding program.

ABNORMAL NUMBERS OF TOES: Polydactylism is a dominant gene. If a cat has it, he or she will pass it on to offspring. That is why you often see, in domestic cats, colonies of polydactyl cats. If the breed you work with does not allow extra toes, any kittens born with extra ones are not desirable for breeding.

Conversely, a cat that has or produces too few toes is also not a desirable cat for breeders to use in their breeding program. This trait appears to be genetic (not surprising) and can be cumulative. There is a reason that breed standards specify the number of toes.

ASYMETRICAL FACIAL STRUCTURE: If cats are allowed to breed randomly, the resulting facial structure is a moderate one with a medium nose, curved profile, and moderate chin. The lower jaw is squarely below the upper jaw and does not protrude or recede. The teeth are strong and stay in the mouth a long time. These cats have moderate sized eyes that do not stick out (protrude). This is nature selecting for animals that can eat well, chew well and see well. The eyes do not protrude and make the animal susceptible to having an eye poked out. Ears are moderate in size and have hair in them to keep out bugs and other matter. Not a pretty picture you say? Nature selects for things that make these animals strong and gives them superior ability to survive. Nature puts survival above a pretty picture.

When breeders selectively breed cats with very long noses or very short ones, with very large and/or protruding eyes, and with jaws that do not squarely sit together, they are not doing this on purpose, but in truth they are selecting for things that will make this animal less able to survive naturally. What we mean to be “pretty” can also sometimes distort tear ducts, nasal passages, and other structural parts of the head and face so that these animals are less able to do things normal animals do. As was stated early in this article, the trick is to select breeding stock that is beautiful and that produces more beautiful offspring without enhancing the detrimental qualities.

Sometimes, especially in the more "extreme" breeds, we see heads that do not match from side to side. One side of the facial structure is full and round and one may be angular and not round (in the Persian) or one eye may be higher in the head than the other (all breeds). These are not desirable traits for breeding stock and should be avoided.

ABNORMAL STERNUM: Cats can be born with an abnormal sternum, which shows itself with the lower portion of the chest bone sticking out – sometimes it pops in and out (called a xyphoid cartilage abnormality). This is not a desirable trait because a sharp blow on this area of the chest could injure the animal. It is also not a desirable trait to put into a breeding program.

In addition, kittens with chests too rounded or too flat are not desirable. These kittens have a hard time growing because the chest cavity is not an appropriate shape for the heart and other organs.

Cats that were flat-chested as kittens should not be used for breeding, even if they appear to grow out of the disorder, as this trait appears to be familial.

ABNORMAL VISUAL PATHWAYS (strabismus, nystagmus): In this abnormality, the visual pathway from the brain to the retina is misrouted; there are problems with depth perception. Strabismus is a squint and nystagmus is involuntary eye movements. These have been reported in Siamese and Himalayans and appear to be associated with forms of albinism, according to the Merck Veterinary Manual (ninth edition). It is important to note that nystagmus and strabismus can be present without abnormality of the visual pathway but can be instead a symptom of the pathway being influenced adversely by something like a nasopharyngeal polyp.

AMYLOIDOSIS: In affected Abyssinians and Somali cats, an amyloidal substance is deposited in organs such as the kidneys, but can be present in the liver, the brain or the digestive system. Symptoms are listlessness, poor coat condition, weight loss, excessive thirst, and excessive urination. In affected Siamese, Burmese, and related breeds insoluble protein called "amyloid" is deposited and affects the liver. Spontaneous liver rupture and hemorrhage can occur, with sudden death the result. The disease appears to be familial, but the mode of inheritance is unknown.

BURMESE CRANIOFACIAL DEFECT (MENINGOENCEPHALOCELE SYNDROME): This recessive defect is a form of incomplete conjoined twinning in which the upper jaw region is duplicated. The head region above the upper jaw does not form properly. Eyes and ears are malformed and there is incomplete closure of the skull. Kittens are born alive but cannot survive. Carriers of this trait may have abnormal skull structure, cleft lip, dermoids (displaced portions of skin), or an abnormality of one or more eyelids. Research is currently underway to identify the gene and develop a test to determine carriers.

CATARACT: A recessive form of inherited bilateral cataracts (opacity of the lens of the eye) has been identified. The cataracts are severe by 12 weeks of age. This abnormality has been reported in British Shorthairs, Himalayans, Persians, Birmans and other pedigreed varieties as well as in domestic shorthairs. Cataracts are opacities of the lens which can cause failing vision or blindness. Some forms appear at birth while others appear in the adult cat. Some forms are

progressive; others are not progressive and can be removed surgically. In the British Shorthair, Himalayan, and Persian an autosomal recessive genetic inheritance is suspected. In the Birman, the inheritance is not known.

CHEDIAK-HIGASHI SYNDROME (OCULOCUTANEOUS ALBINISM): This syndrome is associated with a light bluish colored coat and yellow-green iris (reflects red in photo flash) due to reduced/absent pigmentation of the tapetum (reflective layer) of the eye. Photo-sensitivity is common. The optic nerves are disrupted, causing squinted or crossed eyes. The white blood cells of these affected animals are abnormal because of defective lysosomes. Bleeding time, even after minor surgery or injury, is increased due to platelet abnormalities, and hematomas can form in the tissues. It was first identified in a line of blue-smoke Persian cats. It is believed to be inherited as an autosomal recessive.

CHERRY EYE: The Cherry Eye is a prolapsed gland of the third eyelid. It has been seen in the Burmese cat. The third eyelid gland protrudes and becomes swollen and reddened. It can be surgically repaired. The inheritance is not known, but it is associated with extremely shortened facial structure.

CHYLOMICRONEMIA (LIPOPROTEIN LIPASE DEFICIENCY): Affected cats have a reduced body mass and slow growth rate. This is lethal in homozygous form.

CLEFT PALATE: Cleft Palate is one of the most common congenital defects in cats as well as other animals, and can also have non-genetic causes. The cleft can be in both hard and soft palate. Kittens have difficulty nursing and may develop aspiration pneumonia. It is seen more often in the Siamese family, but can occur in any cat. It is thought to be polygenic, but more frequently is due to environmental factors such as exposure to certain drugs, toxins, or infections during pregnancy.

CORNEAL EDEMA: An apparently inherited form of corneal edema has been reported. Fluid accumulates in the layers of the cornea causing cloudy eyes by about 4 months of age. The condition is progressive. Ultimately, corneal tissues break down and severe bacterial infection follows. The mode of inheritance is unknown.

CORNEAL MUMMIFICATION: Also called focal corneal necrosis or corneal sequestrum, this is a type of focal corneal degeneration with formation of a brown-black plaque often accompanied by ulceration. It is associated with chronic inflammatory conditions and can require surgical repair. This disorder has been reported in Persian, Himalayan, Burmese, Birman, Siamese, and Colorpoint Shorthair (Britain). The genetic mechanism is not known for most breeds but it is suspected to be autosomal recessive in the Colorpoint Shorthair. It is important here to note that the sequestrum can be the result of traumatic injury or herpes virus infection of the eye itself and not necessarily a genetic abnormality.

CRYTORCHIDISM, MONORCHIDISM: Unilateral or bilateral retained testes (cryptorchidism) can be familial, although the mode of inheritance is unknown. Unilaterally affected males may be fertile, but should not be bred from in order to minimize the incidence of this trait in the population. If a male you are planning to use for breeding has one descended testicle or no

descended testicles, or, if the testicles have a difficult time descending, he is not good breeding stock. I think everyone agrees that it is not a desirable trait but additionally, it can be a health issue. A testicle that is not descended still exists. It may be located at the place where testicles begin to develop (high up near the kidney) or it may be near the surface but the structure is abnormal so that it will not stay descended, but it is usually there. These animals are not easy to neuter if the testicle is high up and hard to find. This is not a desirable trait to perpetuate in a breeding program.

CUTANEOUS ASTHENIA (WINGED CAT CONDITION): The skin is excessively loose and fragile due to defects in the collagen. This group of abnormalities is also called dermatosparaxis or Ehlers-Danlos syndrome. The abnormalities result in defects in collagen production. This results in a variety of clinical signs, including loose, hyperextensible, fragile skin; joint laxity; and other connective tissue dysfunctions. These defects have been described in many species, including domestic cats and Himalayans. In domestic cats, the disorder is described as dominant; in Himalayans it is described as recessive.

DEAFNESS: Unilateral or bilateral congenital loss of hearing is associated with the dominant white gene and is caused by a loss of a cell layer in the inner ear which is essential for sound hearing. The trait is most common in white cats with two blue eyes, less common in white cats with only one blue eye, and relatively rare in white cats without blue eyes. This loss of hearing is due to progressive degenerative process occurring in the inner ear. It begins in the first week after birth. It is a dominant white gene and has complete penetrance in white coats with blue eye color in several breeds. It has incomplete penetrance with blue eye color in other cats. Refer to information in the article entitled “The Pigment Parade” elsewhere on this CD.

DIABETES MELLITUS: Diabetes mellitus is due to inadequate insulin production. As with humans, it may be controlled by insulin injection. Symptoms include increased hunger and thirst, increased urine production and sugar in the urine. The risk of diabetes increases with age and obesity.

DISTAL POLYNEUROPATHY: A degenerative polyneuropathy was found in a family of Birman cats. Symptoms begin at 8-10 weeks. Affected kittens fell frequently, tended to stand and walk on their hocks, had exaggerated limb action, and progressive pelvic ataxia.

ENTROPION: Entropion is an Inward turning of the eyelid margin so that eyelashes and hairs rub on the cornea causing conjunctivitis and corneal ulceration. It usually requires surgical repair. It has been reported in the literature in the Persian and related breeds, although it occurs in many breeds, and is thought to be due to mutations in several genes controlling structure of eyelid, fit of globe to socket, and facial skin.

EPIBULAR DERMOIDS: Reported in a family of Birmans and also seen in Burmese and American Shorthair cats, epibular dermoids are skin-like growths that are hairy, pigmented and attached to the conjunctiva at the corner of the eye or on the nose. The hairs of the dermoid area cause irritation and inflammation, necessitating their surgical removal. The cause of the genetic abnormality is not known.

EPISODIC WEAKNESS: This disease manifests between 4 - 10 months of age (average 7.4 months). The cat appears normal until an attack is triggered by factors such as excitement or mild stress. During an episode, the head is held close to the chest when walking or resting, When walking, the head nods up and down and the forelegs are stiff, straight, and high stepping while the hind legs flex normally, but are abnormally splayed. The pupils become dilated and the claws extended.

ENDOCARDIAL FIBROELASTOSIS: A severe thickening of the endocardium of the heart causes changes in the left side of the heart and leads to heart failure at a young age. There is no treatment. It has been reported in both Siamese and Burmese cats and the heritability is not known.

EYELID AGENESIS (lid coloboma): This congenital eyelid abnormality results in incomplete development of eyelids. It often requires reconstructive surgery. It has been reported in Burmese cats and the genetic inheritance is not known.

FLAT-CHESTED KITTEN SYNDROME: Kittens are born with a normal appearance, but within the first few weeks of life the kitten's chest appears concave, compressed or flattened instead of convex due to abnormalities of the ribs at the costochondral junction. Curvature of the spine may also be present. In more severe cases the kitten has breathing difficulties, is distressed and has stunted growth. Internal organs are dislocated (severity depends of degree of flat chest). Kittens that are only mildly affected can recover and the chest appears to become normal. Severe cases result in death. Flat chest has been reported in Burmese, Tonkinese, Bombay, and other breeds. It is suspected to be polygenetic or autosomal dominant with incomplete penetrance.

GANGLIOSIDOSIS GM1 and GM2: An autosomal recessive lysosomal storage disease, where the lack of a critical enzyme leads to the build-up of precursor molecules in the structures of the cell known as lysosomes. This causes a degenerative disease of the brain and spinal cord due to a deficiency of beta-galactosidase (GM-1) or beta-hexosaminidase (GM-2). A head tremor and hind limb tremor begins at 2-3 months of age that becomes increasingly severe. By adulthood, seizures and loss of vision occur. GM1 shows up later and progresses more slowly than GM2. The disease is always fatal and there is no known treatment available at this time. The disease has been reported in Korats and Siamese. There is a DNA test for this abnormality available.

GLOBOID CELL LEUKODYSTROPHY (KRABBE DISEASE): Neurological, recessively inherited disease. Affected kittens develop a tremor, weakness and lack of coordination of the back legs by 5-6 weeks. The poor coordination progresses to the forelegs due to degenerative changes in the brain. Loss of bladder control occurs by about 12 weeks and the hind limbs become rigid and straight. By 15 weeks there is hind limb paralysis and by 21 weeks respiratory problems lead to death.

GLYCOGEN STORAGE DISEASE TYPE IV: This is a recessive lysosomal storage disease cause by a deficiency of a glycogen branching enzyme. Abnormal glycogen accumulates, affecting the nervous system, muscles and heart. Kittens may have cardiopulmonary collapse and die at birth or develop progressive neuromuscular degeneration. There is no known treatment for this

abnormality, but there is a genetic test available to detect carriers and the abnormality has been eliminated from today's Norwegian Forest Cats.

HAGEMAN FACTOR DEFICIENCY: A dominant mutation that causes a deficiency of a blood clotting factor that results in a mild bleeding disease.

HEMOPHILIA A and B: This sex-linked disease is characterized by prolonged bleeding after injury or surgery, poor blood clotting and hematomas under the skin. Affected cats can survive if care is taken to prevent injury. The B type is less severe than the A type.

Hemophilia A: Clotting Factor VIII deficiency leads to spontaneous bleeding or prolonged clotting times. Mainly British Shorthairs are affected, but it has been reported in Siamese, Persians and Himalayans. Control of bleeding episodes can be accomplished using transfusions of clotting factors or whole blood from non-affected animals. These animals should not be used in breeding programs.

Hemophilia B: Clotting Factor IX deficiency leads to spontaneous bleeding or to prolonged clotting times. It is sex-linked (found on the X chromosome) so females can be carriers, and males affected. Mainly British Shorthairs are affected, but it has been reported in Siamese, Persians and Himalayans. Control of bleeding episodes can be accomplished using transfusions of clotting factors or whole blood from non-affected animals. These animals should not be used in breeding programs.

HIP DYSPLASIA: Abnormal development of tissue in the hip results in fibrous tissue replacing bone. It can lead to debilitating arthritis, weakness in the hind quarters. Problems such as hip dysplasia are found in many (if not all) cat breeds, and have a genetic component (probably polygenic), but also an environmental component, and perhaps a behavioral one as well (which may also be partially determined by the genes). The hip joint is not properly formed and sometimes the muscle structure that holds these joints together is also weakened. The result is that hips and legs are not straight or hips and knees wobble in and out of position. We call some of the resulting positions "cow hocks", "hips out of joint" or other terms. Mild cases can go undetected. There are programs like Penn Hip (University of Pennsylvania) or OFA that will screen breeding stock and provide certification of good hips. In any case, these are not desirable traits, and selective breeding away from these traits is necessary to maintain the structural integrity of the breed.

HYDROCEPHALUS: Cases of hydrocephalus due to a recessive gene have been reported, although this can also be caused by a random error in embryonic development. Affected kittens are born large and bloated. The head is swollen and fluid-filled causing pressure on the brain and progressive debility. There may be other cranial defects such as cleft palate, hare lip or deformed feet. The condition should be considered lethal though there are reported cases of hydrocephalus that have responded to surgery. Literature reports have been made concerning Siamese and Persians, but certainly this error in development could occur in any breed or in domestic cats.

HYPERCHYLOMICRONEMIA (HYPERLIPOPROTEINEMIA): Kittens with this recessive disorder grow normally but have persistent lipaemia (excessive fatty substances in the blood). By 8 or 9

months of age they become unable to move their eyelids or chew properly. They cannot extend their toes and lose the knee reflex. Multiple hematomas affect the peripheral nerves, causing loss of sensation. Some affected cats exhibit facial paralysis, limb paralysis, muscle atrophy and laryngeal paralysis resulting in breathing problems. Some symptoms may be reduced following 2-3 months of a low fat diet, but the long-term prognosis is generally poor.

HYPERTROPHIC CARDIOMYOPATHY: The most common heart disease in cats, HCM is characterized by progressive enlargement of the heart and thickening of heart muscle, particularly of the left ventricle. A dominant mode of inheritance has been established in some breeds and a causative mutation in the myosin binding protein C gene has been identified in the Maine Coon breed specifically. There is a DNA test for Maine Coon cats

Sudden death has been noted in cats only a few years old although affected cats may live for 10 years or more before developing symptoms including exercise intolerance, fatigue, fainting, fluid collection in the lungs, abdomen, and limbs, or blood clots that arise in the heart and travel to the kidney, brain, or legs.

Ultrasound screening is a common tool utilized by veterinarians to see this disorder, though it can be difficult to diagnose this condition. .

It is seen in the American Shorthair where it is believed to be an autosomal dominant. However, a test is not available in this breed at this time.

It is seen in Persians where two forms of disease appear to exist: one is a typical hypertrophic cardiomyopathy and the second is hypertrophic obstructive cardiomyopathy (also called asymmetrical septal hypertrophy). Sudden death or death under anesthesia can occur. Heritability is not known in the Persian and a test is not available at this time.

It has been seen in the Ragdoll and the Norwegian Forest Cat and studies are currently underway to define the issue in this breed.

It is reported in the Sphynx breed and the incidence and genetic heritability is under study.

HYPEROXALURIA (L-GLYCERIC ACIDURIA): Acute renal failure due to this recessive mutation occurs between 5-9 months old. Cats increasingly become depressed, anorexic, dehydrated and weak. Other symptoms include a crouching, cow-hocked stance, reluctance to stand or walk, and a depressed patellar reflex. The kidneys are painful and kidney failure is caused by deposited oxalate crystals in the kidney tubules. The liver and spinal cord are also affected. Heterozygous cats may have intermediate liver levels of the enzyme D-glycerate dehydrogenase, allowing carriers to be identified.

HYPOKALEMIA: Low blood levels of potassium lead to muscle weakness, abnormal gait. The deficiency can be treated with potassium supplements. It has been reported in the Burmese cat and is thought to be autosomal recessive.

HYPOTHYROIDISM (defective thyroid peroxidase enzyme): Juvenile-onset hypothyroidism can be caused by a defective thyroid enzyme. Kittens have stunted growth and physical changes. Early treatment with thyroid hormone is possible. This has been reported in the Abyssinian and is thought to be autosomal recessive.

HYPOTRYCHOSIS: This disorder is a form of alopecia (hairlessness) and includes the presence of less hair than normal. In the Sphynx cat there appears to be no detrimental effect. The Devon Rex appears to have follicular dysplasia, in which certain colors are more apt to show the hairlessness. In Birmans and Siamese, the disorder has been reported to be an autosomal recessive. The Siamese form appears to be non-lethal. Two Birman types have been noted. The "Redcar" form affects kittens that die by 13 weeks of age; the "Switzerland" form is associated with thymic aplasia (a type of immune system failure).

LUXATING PATELLA: The patella (kneecap) is displaced from its normal position either by force or spontaneously. This may recur if the trochlear groove is shallow or malformed. It may correct itself and cause only temporary discomfort or it may require surgery if the condition recurs or causes lameness. Cats with luxating patella have a greater tendency to hip dysplasia than those without.

MANNOSIDOSIS: Mannosidosis is an enzyme deficiency that affects the central nervous system. Most kittens with mannosidosis are either stillborn or die at birth. Those that survive show symptoms during the first few days or weeks. Symptoms are general lethargy and diarrhea, progressing to tremor and ataxia. Affected kittens appear unable to stand properly. The voice becomes weaker and an enlarged liver causes a swollen belly. There is a genetic test available for this abnormality.

MEGAESOPHAGUS: Some cases of megaesophagus appear to have a hereditary link. The esophagus is dilated and peristalsis is impaired so that swallowed food may be regurgitated. This becomes apparent after weaning. The condition is also called eosophageal achalasia, esophageal dilatation, esophageal hypomotility and esophageal neuromuscular disease. The condition can be managed by elevating the food bowl so that gravity assists in getting food into the stomach. If untreated, weight loss and malnutrition are likely.

MUCOPOLYSACCHARIDOSIS 1 and 6: There are two biochemically distinct forms of mucopolysaccharidosis caused by different mutations of the same gene, but the disease is very similar in both types. These recessively inherited enzyme deficiencies cause grossly abnormal neurons in the brain and spinal cord. The facial profile of affected cats is altered and affected cats have a short, broad nose, depressed nasal bridge, prominent forehead, small ears and opacity of the cornea. Affected cats sit crouched with spread forelegs. The cervical vertebrae are unusually wide, asymmetrical and frequently fused. The breast-bone (sternum) is abnormally concave. Enlarged liver and spleen may cause a swollen belly. A deficiency of this enzyme can be detected in heterozygous cats, allowing carriers to be detected.

NEONATAL ISOERYTHROLYSIS AND TRANSFUSION REACTIONS: There are three blood types found in cats: by far the most frequent is Type A. Blood type B is recessive to Type A. And there is a small minority of cats who are Type AB. About ½ of the pedigreed cat breeds show some evidence of Type B blood types. Some breeds (including the Birman, British Shorthair, Devon and Cornish Rex) have over 25% of the cats with B blood type.

Two problems arise with the different blood types:

Breeding issues -

Type A kittens born to type B queens can become ill within the first three days of life. The red blood cells in these kittens break down due to the antigenic activity in the colostrum of the queen. The cells are excreted in the urine giving the urine a black or rusty look (due to the iron in the hemoglobin that is excreted). The treatment for this problem is to remove the kittens at birth or as soon as the black urine is noted and hand feed these kittens for three days. Then they can be returned to the mother safely. Many breeders favor knowing the blood types of all of their breeding stock if this is an issue in their breed. Many laboratories can do this testing, and there are kits available for breeders to do this testing on their own newborns.

Transfusion Reactions-

If cats with blood type B are transfused with blood type A blood, they will have an almost immediate (serious) reaction to the antigens in the blood type A blood.

Most veterinary hospitals can type a cat prior to a transfusion to eliminate this problem.

The genes that cause these differences in blood types are under study today.

NEUROAXONAL DYSTROPHY: This degeneration of neurons of the brain stem is caused by a recessive gene. It is associated with a pale coat color similar to non-agouti lilac. Affected kittens show head-nodding at 5 weeks old; more pronounced head-shaking at 6 weeks and have an uncoordinated gait at 8 weeks. These symptoms worsen as the disease progresses. Sight and hearing may deteriorate and growth is stunted.

NEUTROPHIL GRANULATION ANOMALY: Abnormally formed white blood cells appear to function normally. This disorder is not associated with any medical problems noted at this time. It has been reported in Birmans, Abyssinians and Persians and is thought to be autosomal recessive in Birmans.

OSTEODYSTROPHY: This disorder is seen in the Scottish Fold and is associated with a short, thick, inflexible tail and painful deformities of limb extremities. This is an autosomal dominant with variable expression.

PATENT DUCTUS ARTERIOSUS (PDA): This disorder is caused by failure of a fetal blood vessel, the ductus arteriosus, to close after birth. Kittens have a distinctive heart murmur. Most cats develop heart failure. This has been reported in the Siamese and several other breeds. The heritability is not known.

PELGER-HUET ANOMALY: This dominant mutation causes abnormal segmentation of the nuclei of granulocytes (one of the several forms of white blood cell), but does not appear to adversely affect health.

POLYCYSTIC KIDNEY DISEASE (PKD): The most common heritable disease of man is also seen in cats. The form seen in Persian and related breeds is caused by a dominant mutation and appears to have an incidence of almost 40% in this breed. Kidney function deteriorates with age and kidney disease occurs between 3 and 10 years of age, with an average of seven years. Kidney cysts are evident through ultrasound scans by 8-10 months of age, although severity and progression of the disease varies widely between individuals. Mildly affected cats may throw more severely affected offspring and vice-versa. The causative mutation of the PKD-1 gene has been identified and a DNA test is available for Persian and related breeds. A recessive form of PKD also exists. Affected kittens are born with enlarged abdomens and death occurs at 6-7 weeks of age. Upon necropsy, enlarged cystic kidneys and cystic bile ducts of the liver are seen.

PORPHYRIA: Porphyrins are heme precursors that are generated in the bone marrow. A dominant mutation results in the production of excessive amounts of porphyrins and their deposition in body tissues such as the skin, bones and teeth. Excess porphyrins are eliminated in the urine. The teeth appear to be unusually discolored and the urine turns bloody. These symptoms are usually evident at an early age. Under UV light, the porphyrins in the teeth and bones result in bright pinkish-red fluorescence. A second form of porphyria has been identified with additional symptoms of anemia and lethargy, but the mode of inheritance was not established.

PORTOSYSTEMIC SHUNT (portocaval or liver shunt): This is caused by abnormal vessels that allow blood to bypass the liver. It is sometimes associated with enlarged kidneys and heart problems. Symptoms include excessive salivation, liver disease and stunted growth seen in young cats. Males more often affected and surgical correction is necessary. It is reported in Persians, Siamese and other breeds and its inheritance is not known at this time.

PROGRESSIVE RETINAL ATROPHY (PRA): This is a degenerative disease of the retina resulting in the loss of vision. The age of onset and progression of the disease may vary. Typical signs are dilated pupils, increased reflection of light from the back of the eye, and behavior associated with poor vision. In a recessive form identified in the Persian breed, blindness is apparent by 12-15 weeks. In another form, signs are apparent at 18-24 months with advanced degeneration by 3-4 years of age. A variety of causative gene mutations appear likely.

In Abyssinians, two forms have been seen, one from Sweden (autosomal recessive) and the second in England (autosomal dominant). Tests are available for kittens and young adult cats. In fact, in Europe, Abyssinians are tested before they are bred.

A form of PRA has also been reported in Siamese in Europe. In the Siamese, the disorder is not usually detected until two years of age or older and the heritability is not known.

PYLORIC STENOSIS (PYLOROSPASM): This malfunction of the lower opening of the stomach can be diagnosed through x-rays using barium as a contrast medium. Symptoms begin after weaning and include persistent, sometimes violent, vomiting following meals. The inability to retain food results in poor growth and stunting. There appears to be a genetic component to the condition, but the mode of inheritance is unknown.

PYRUVATE KINASE DEFICIENCY: Pyruvate kinase (PK) is an enzyme critical to energy production in the red blood cell. If these cells are deficient in PK they are unable to sustain normal cell

metabolism and are destroyed prematurely by the cat's body. The primary symptom is hemolytic anemia with a regenerative response. Other symptoms include exercise intolerance, weakness, heart murmur and enlarged spleen. A recessive mutation for PK deficiency has been identified in Abyssinian and Somali cats and a DNA carrier test is available in these breeds.

SEBORRHEA OLEOSA: This is a chronic skin condition with scaling, excessive greasiness, alopecia and dermatitis. The signs appear in kittens and the disease is hard to control. It has been reported in Persian cats and is thought to be autosomal recessive.

SPASTICITY (MUSCULAR DYSTROPHY): A hereditary muscular disorder has been identified in the Devon Rex and Sphynx breeds. Symptoms usually develop between 4-7 weeks though some kittens show no symptoms until 12-14 weeks. Affected kittens hold their shoulder blades high and their neck arched downwards. When resting, the body lies flat with the head held to one side. The arched neck interferes with feeding and drinking. Esophageal hypomotility and megaesophagus are also present. The condition worsens with age and the cat rests more often, either lying flat with the head to one side or leaning against an upright object. There is no known treatment, but there is a test for the condition that has been used successfully to determine if the condition is muscular dystrophy.

SPHINGOMYELINOSIS (NIEMANN-PICK DISEASE): This is a recessive lysosomal storage disease, where the lack of a critical enzyme leads to the build-up of precursor molecules in the structures of the cell known as lysosomes. This causes a severe neurological disease in which affected kittens lose interest in their surroundings, stop eating, and develop a tremor that leads to severe ataxia. The liver and spleen may be enlarged. This abnormality has been reported in the literature in Siamese and related cats. Carriers can be identified through a blood test to identify the enzyme deficiency.

SPINAL MUSCULAR ATROPHY: SMA is a disorder caused by death of spinal cord neurons that activate skeletal muscles of the trunk and limbs. Loss of neurons in the first few months of life leads to muscle weakness and atrophy that first becomes apparent at 3-4 months of age. Affected kittens develop an odd gait with a sway of the hindquarters and stand with the hocks nearly touching. By 5-6 months of age, severe weakness in the hindquarters is apparent and muscle mass is reduced. Affected cats are not in pain and most live very comfortably as indoor cats for many years. The genetic cause of this recessive spinal muscular atrophy in Maine Coon cats, involving a large deletion on cat chromosome A1 removing two genes, was determined in May 2005 and a DNA test is available.

TAILLESSNESS: The tailless gene is associated with several defects which can affect the entire spinal column, leading to changes in vertebrae and sometimes defects in nerve supply to bowel and bladder; occasionally associated with spina bifida and deficits in nerve supply to hind legs. It is an autosomal dominant gene with incomplete penetrance (variable length of tail present). Manx breeders have been successful in not breeding tailless to tailless.

TREMORS AND ATAXIA: A variety of breeds appear to have heritable forms of neurological problems that cause a continuous, whole body, tremor and staggering gait commencing at 2-4

weeks old. Affected kittens roll and bob in an undulating fashion and the tail may weave in circles (possibly in an attempt to balance the kitten). Unlike cerebellar hypoplasia caused by panleukopenia virus exposure during pregnancy, the cerebellum is normal upon necropsy. In some forms, the kittens may outgrow this condition; in other forms, it is progressive.

UMBILICAL HERNIA AND CLEFT PALATE: These mid-line defects are caused by the incomplete merging of the right and left sides of the embryo during early development. In its most extreme form, herniation can cause a kitten to be born with its intestines outside of the body. These congenital defects can be familial, although a precise mechanism of inheritance is unknown. They may also be caused by environmental factors such as exposure to toxins, nutritional deficiencies, or exposure to some medications or viruses during pregnancy.

VITAMIN-K DEPENDENT COAGULOPATHY: Multiple clotting factors are impaired leading to spontaneous bleeding and hemorrhages. Sudden death sometimes occurs. It is treated with vitamin K supplementation. This has been reported in Devon Rex and is thought to be autosomal recessive.

VON WILLEBRANDS DISEASE: This Clotting Factor Deficiency (a form of factor VIII deficiency) leads to bleeding tendencies and spontaneous hemorrhages. Treatment is only supportive. It has been reported in the Himalayan and its heritability is not known.

SCREENING FOR FELINE HERITABLE DISEASES

Disease/Test	Breeds Testable	Type of Test
Gangliosidosis GM1/GM2	Korat, Siamese	DNA
Glycogenosis (GSD) Type IV	Norwegian Forest Cat	DNA
Hip dysplasia	Any breed	X-ray
Hypertrophic Cardiomyopathy	Maine Coon	DNA
Hypertrophic Cardiomyopathy	Any breed	Ultrasonography
Mannosidosis	Persian, Domestic Shorthair	DNA
Mucopolysaccharidosis (MPS) VI	Siamese, Domestic Shorthair	DNA
Mucopolysaccharidosis (MPS) VII	Domestic Shorthair	DNA
Mucopolysaccharidosis (MPS) (other forms)	Any Breed	Chemistry
Patellar subluxation	Any Breed	X-ray
Polycystic Kidney Disease	Persian and related breeds	DNA
Polycystic Kidney Disease	Any Breed	Ultrasonography
Progressive Retinal Atrophy	Any Breed	Opthamological exam
Pyruvate Kinase (PK) Deficiency	Abyssinian, Somali	DNA
Spinal Muscular Atrophy	Maine Coon	DNA
Sphingomyelinosis	Any breed	Chemistry

Genetic testing is in its infancy. The technology that made the feline genome project a reality has been in existence for less than 20 years. Once the technology for polymerase chain reaction (PCR) and DNA Analysis was perfected and made reliable, the genome components were identified. This part of the project has been completed.

Now scientists are focusing on identifying particular genes that are linked to specific abnormalities. The easiest of those are the clearly dominant genes linked directly to specific issues, such as the gene responsible for polycystic kidney disease in the cat. The recessive genes are also important and identifiable. An example of this is the gene responsible for the glycogen storage disease which was found in Norwegian Forest Cats. The hardest type of abnormality is the one that is caused by several genes (polygenic) and could be combined with environmental factors.

Another thing that is important to understand is that an abnormality in one breed may be caused by a recessive gene and in another breed the same abnormality may be dominant. This is because genes act in combinations during development and the abnormality may occur in different stages of development in different breeds.

At the time of this writing, there are three research labs in the United States, one in Europe and one in Australia whose work is concentrated in the identification, characterization, development and making tests available to the public for specific genetic abnormalities. These labs have col-

lected DNA samples from breeders of cats the world over to give them the necessary DNA to look at colors, patterns, basic inheritance, as well as genetic abnormalities and diseases. You, the breeder, have helped to make these tests available and we hope that you will continue to contribute to these research facilities.

If you find an abnormality that you and your veterinarian do not understand, these research testing laboratories can help you to determine what the abnormality is.

UNITED STATES:

CatGENES.org (DNA Diagnostics & Texas A&M University)

Tests available, using VeriSNP™ Universal Genetic Evaluation:

Albinism
B Blood Group
Black coloration
Burmese (gene associated with color shading)
Chocolate-Brown
Cinnamon-Red
Dilute Coloration
Hair length (3 of the 4 markers for hair length are available now and the 4th one will be available at a later date.)
Hypertrophic Cardiomyopathy (HCM) (Maine Coon)
Hypertrophic Cardiomyopathy (HCM) (Ragdoll)
Identity fingerprint
Mucopolysaccharidosis MPSM (Lysosomal Storage Disease)
Mucopolysaccharidosis MPS1 (Lysosomal Storage Disease)
Paternity identity (parentage verification), when needed
Polycystic Kidney Disease (PKD)
Sex Markers
Siamese points

ADDRESS	CONTACT INFORMATION
DNA Diagnostics, Inc. P.O. Box 455 Timpson, TX 75975	Genetic Testing: Email info@dnadiagnostics.com General Questions: Phone: (936) 254-2228 Available tests and submission forms: http://www.CatGENES.org

Texas A & M University – Dr. Gus Cothran, VIBS, CVM, Investigator

ADDRESS	CONTACT INFORMATION
Texas A&M University TAMU 4458 College Station, TX 7783-4458	Genetic Testing: Dr. Gus Cothran VIBS, CVM Available tests and submission forms: http://www.CatGENES.org

University of Pennsylvania (Philadelphia) – Urs Giger, DVM, Investigator
Tests available through PennGen, a testing laboratory at U. Pennsylvania

At this time, University of Pennsylvania (PennGen) performs the following tests:

Cystinuria (any cat breed)
Erythrocyte Osmotic Fragility (OF) Test (any cat breed)
Erythropoietin Concentration (any cat breed)
Feline blood typing (any cat breed)
Glycogenosis (GSD) Type IV (Norwegian Forest Cat)
Karyotyping for Chromosomal Disorders (any cat breed)
Mannosidosis (Persian, Domestic Shorthair)
Metabolic Screening (any cat breed)
Mucopolysacharidosis (MPS) VI (Siamese, Domestic Shorthair)
Mucopolysacharidosis (MPS) VII (Domestic Shorthair)
Other Special Erythrocyte Studies (e.g., enzyme, hemoglobin and membrane defects in any cat breed
Platelet Aggregation Studies (any cat reed)
Polycystic Kidney Disease (Persian)
Pyruvate Kinase (PK) Deficiency (Abyssinian, Somali, Domestic Shorthair)
Special Coagulation Studies (any cat breed)
Special Leukocyte Studies for Immunodeficiencies (any cat breed)

ADDRESS	CONTACT INFORMATION
University of Pennsylvania School of Veterinary Medicine PennGen/Section of Medical Genetics Veterinary Hospital 4006 3900 Delancey Street Philadelphia, PA 19104-6010	Genetic Testing: Email PennGen@vet.upenn.edu Phone (215) 898-3375 or (888) PENNGEN General Questions: Phone: (215) 898-8894 Fax: (215) 573-2162 Available tests and submission forms: http://w3.vet.upenn.edu/research/centers/penngen/services/alldiseases_breed.html

University of California (Davis) – Leslie Lyons, PhD, Investigator

Tests available through Veterinary Genetics Laboratory (VGL), a not-for-profit arm of U. C. Davis.

The University of California (Davis) VGL laboratory can perform the following tests:

Blood Typing - feline
Coat colors – feline (Agouti, Chocolate/Cinnamon, Pointed)
Forensic testing – feline
Hypertrophic Cardiomyopathy (Maine Coon Cat)
Parentage testing – feline, including gender
Polycystic Kidney Disease (Persian, Exotic)

ADDRESS	CONTACT INFORMATION
Veterinary Genetics Laboratory One Shields Avenue Davis, CA 95616-8744	Customer Service: Phone (530) 752-2211 Fax (530) 752-3556 Cat Tests: http://www.vgl.ucdavis.edu/service/cat/index.html

Washington State University - Kate Meurs, DVM, Investigator

This research laboratory is currently (2006) studying hypertrophic cardiomyopathy in the Ragdoll, Norwegian Forest Cat, American Shorthair, and Sphynx.

ADDRESS	CONTACT INFORMATION
Washington State University College of Veterinary Medicine PO Box 647010, Pullman, WA 99164-7010	Phone 509-335-9515 Veterinary Cardiac Genetics Lab http://www.vetmed.wsu.edu/deptsVCGL/

THE NETHERLANDS:

ADDRESS	CONTACT INFORMATION
Faculty of Veterinary Medicine University of Utrecht Yalelaan 17 3584 CL Utrecht The Netherlands	Phone 030 253 90 00 Fax 030 253 77 27 http://www.vet.uu.nl/viavet/ Advances in Veterinary Medicine http://www.vet.uu.nl/viavet/viavet_english/onderzoek/onderzoeksprogrammas/avm

AUSTRALIA:

Gribbles Veterinary Pathology can perform Polycystic Kidney Disease (PKD) DNA testing.

ADDRESS	CONTACT INFORMATION
Gribbles Veterinary Pathology 1868 Princes Highway Clayton Victoria 3168 Australia	**Enquiries** vets@gribbles.com.au Phone +61 3 9538 6777 **Helpdesk** Phone 1300 307 190 **DNA Testing:** http://www.gribbles.com.au/dna_catTest.htm