In order to understand the genetic traits and disorders that we see in our patients, we have to understand the genetic forces and influences that shaped them. Around ninety-five percent of our feline patients are random-bred (domestic short or long-haired), with the rest being pedigreed cats. Our canine patient population tends to vary more with societal changes, but about half are purposefully bred (purebred or designer bred), and the rest are random-bred mixed breed dogs.

The genetic similarities and differences between these types of dogs and cats are based on their evolutionary development and the selective pressures placed on them through purposeful breeding. One must understand the population dynamics involved in the evolution of species, and then the artificial selection that creates breeds.

Species develop through natural selection. Any genetic changes that occur within a population that improve the chance of survival and ability to reproduce in the populated environment will drive evolution. Lines that do not evolve and become disadvantaged will diminish in influence, and often die out.

The development and proliferation of “specialists” who are more capable of living and reproducing through natural selection results in a loss of genetic diversity through the disadvantaged. Any selection, whether natural or artificial will cause a loss of genetic diversity. This loss is not detrimental to the population if it is directly related to increasing its superiority.

*Canis familiaris* developed to live alongside man with a plasticity of behavior and morphology to perform various tasks. These behaviors involved honing their natural abilities at hunting, guarding, hearing, scenting and protection. Through artificial selection of individuals that were best at performing the associated task, lines of dogs developed that differentiated themselves from others. Morphological features that improved these abilities increased the physical difference between lines such as; the speed and ability of hunting dogs versus the strength and durability of dogs of war (mastiff breeds). The later separation of task-associated groups into breeds occurred with further restrictions along conformational and behavioral standards.

*Felis catus* developed to live alongside man for its ability at rodent control and companionship. The development of breeds occurred through artificial selection for body type, color, coat type, behavior and other conformational aspects.

**BREED FORMATION**

Some dog and cat breeds began as inbred populations from limited founders that expanded their populations over time. Others began as outbred populations with a working or conformational phenotype.

The pedigree record of a breed at its inception may show individuals of unknown ancestry, or just individuals that fit the conformational or working standard of the breed. These are the breed’s foundation stock. It is only at a time after an official “establishment” of a breed that a
stud-book is assembled, and soon closed to additional individuals of unknown ancestry. Some cat breeds maintained open stud books for a period of time that allowed for the continued registration of cats adhering to a conformational phenotype. For example, if a cat had the “van” pattern of a Norwegian Forest Cat, it could be registered as a Norwegian Forest Cat. This allowed added diversity to their gene pools. With closed stud books, no new genetic material is available for breed gene pools. Therefore, the genes that are present in the breed can only be lost, and not gained.

When original breed records are examined, it is found that several ancestral family lines during breed formation are often abandoned due to the expression of deleterious or undesirable traits. It is only the lines that produce the desired characteristics and thrive through matings and generations of breeding that become the mainstream ancestral “founders” of a breed. Some breeds are formed through the cross-breeding of individuals from other established breeds. These individuals would be members of established breeds that have already gone through the original breeding and purging process.

Breeds do not have the same population dynamics of natural populations. With breed populations, a much smaller percentage of individuals reproduce to create the next generation. Population dynamics must allow that the individuals chosen for breeding represent the quality traits of the breed, and that these quality traits are not lost through genetic drift or abandonment of quality lines. The rest of the population is lost to the gene pool. There will always be a loss of genes and genetic diversity that results in fixation of traits and homozygosity due to selection.

Regardless of the background of the founders, low effective population size and consequently high inbreeding coefficients are a natural consequence of breed development. Inbreeding coefficients show the genetic relatedness of the parents of individuals. Averaged breed inbreeding coefficients calculated back to breed founders can only increase over time, unless importation from unrelated stock is added to the gene pool. Averaged breed inbreeding coefficients calculated on only the most recent 10 generations will go down from generation to generation in an expanding population; where the average relatedness of breeding pairs is less than the previous generation.

The popular sire syndrome is the single most influential factor in restricting breed gene pool diversity. This is when breeders are concentrating on popular sires or sire lines. In these situations, other quality male lines are abandoned and (genetic diversity) lost to the breed gene pool in exchange for a rapidly increasing influence of the popular sire.5

Modern breeds of cats and dogs have gone through the above mentioned genetic selection, and are in various stages of expanding their population and gene pools. Some breeds may have small effective population sizes and high average inbreeding coefficients. However, if their offspring are generally healthy their population can grow and expand. They are at stages of breed development where more populous breeds were earlier in their development.

Population expansion is an important aspect of breed development and maintenance. It allows the creation of new “family lines” and within-breed diversity. Population contraction is detrimental to breed maintenance due to the loss of quality breeding lines and genetic diversity. Healthy breed gene pools require expanding, or large stable populations.
MOLECULAR GENETIC ANALYSIS OF BREEDS
The process of breed formation creates “selective sweeps” where large chromosomal segments surrounding breed-defining genes become homozygous and fixed in the population. These include selected genes controlling phenotypes for; size, coat color and texture, behavior, skeletal morphology, and other breed-specific characteristics. Similar selective sweeps are found in cattle breeds.

Molecular genetic studies of the chromosomal structure of breeds show these large haplotype blocks (identical sections of chromosomes) and linkage disequilibrium (LD) representing the results of inbreeding and purging during breed development. Studies of dog breeds estimate that they lose on average 35% of their genetic diversity through breed formation.

Molecular genetic studies of breeds document the homozygosity that mirrors the pedigree-based total inbreeding coefficients and common ancestral relationship coefficients. These changes occur due to selection and are an expected prerequisite and consequence of breed formation.

GENETIC DISEASES AND DISORDERS
The most common genetic disorders seen across all dogs and cats, regardless of breed or mixed breed status, are those caused by evolutionarily ancient mutations that preceded the separation of breeds. In dogs, these include liability genes for; allergies, hip and elbow dysplasia, inherited cancers, patella luxation, non-struvite bladder stones, hypothyroidism, mitral valve disease, inflammatory bowel disease, diabetes mellitus, retained testicles, umbilical hernias, and several identified single gene mutations.

The same ancestral autosomal recessive mutation for the progressive rod cone degeneration (prcd) form of progressive retinal atrophy (PRA) is found in the American Cocker Spaniel, American Eskimo Dog, Australian Cattle Dog, Australian Shepherd, Bolognese, Chesapeake Bay Retriever, Chinese Crested Dog, English Cocker Spaniel, English Shepherd, Entelbucher Mountain Dog, Finnish Lapphund, German Spitz, Giant Schnauzer, Golden Retriever, Karelian Bear Dog, Kuvasz, Labrador Retriever, Laaponian Herder, Markiesje, Norwegian Elkhound, Nova Scotia Duck Trolling Retriever, Poodle (Toy, Miniature, & Standard), Portuguese Water Dog, Silky Terrier, Schipperke, Spanish Water Dog, Stumpy Tail Cattle Dog Swedish Lapphund, and Yorkshire Terrier. This list continues to grow as more breeds are discovered with the same defective gene. The question is not, “Which breeds carried this defective gene during their development”, but “Which breeds did not lose this defective gene during evolutionary development.” Similar findings are found with the ancient common mutations for; lens luxation, exercise induced collapse (EIC), choroidal hypoplasia, degenerative myelopathy, multifocal retinopathy (cmr1), and hyperuricosuria (SLC2A9).

In cats, common genetic disorders include liability genes for; inflammatory cystitis and feline urologic syndrome, diabetes mellitus, lymphoplasmacytic gingivostomatitis, non-struvite bladder stones, allergies, eosinophilic skin disease, inflammatory bowel disease, and identified single gene mutations such as polycystic kidney disease, and others. Genetic disorders can also be specific to a single breed, or group of related breeds due to mutations that occurred later in evolutionary development. See “Common Genetic Disorders in Dogs and Cats: Diagnosis & Management.”
Deleterious genes can increase in frequency with natural as well as artificial selection. More “lines” of naturally occurring species have died off due genetic disorders or diminished fitness than those that have survived. All individuals carry some deleterious mutations. As individuals who carry quality traits propagate, they will also propagate their deleterious mutations. Through the founder’s effect, these mutations can become breed-related disease if they are disseminated and increase in frequency.

Studies show that genetic health is not correlated to the genetic diversity of the breed, the population size, or inbreeding, but to the accumulation and propagation of specific disease liability genes. Some breeds have more issues of specific genetic diseases with homozygosity and others do not. This depends on the genetic load of deleterious recessive genes in the breed gene pool. A molecular genetic study of lymphoma susceptibility in Golden Retrievers showed that liability is individual and not just a breed risk. Some breeds may show classic signs of “inbreeding depression”; i.e., decreased litter size, increased neonatal mortality, or shorter average life spans due to the homozygous expression of specific deleterious genes that cause specific disease. Direct selection against these genes and phenotypes is required to improve breed health.

SELECTION FOR DISEASE RELATED PHENOTYPES
The health and vitality of a breed depends on its ability to live, reproduce, and perform the expected function determined by man, unbridled by genetic disease. Some hereditary disorders and disease-predisposing phenotypes have been actively selected for by breeders. These include direct selection, as well as disorders linked to traits that have been selected for. The most evident and widespread is the brachycephalic syndrome observed in the Bulldog, Pug, French Bulldog, Pekingese, Boston terrier, Lhasa Apso, Shih Tzu, and also in Persian and Himalayan cats. This syndrome can cause respiratory distress and death due to a restriction of oxygen flow, chronic dermatitis and corneal ulceration from excessive facial skin folds. Other extreme phenotypes can include excessive skin, excessive skin folds, excessive hind limb angulation, excessive size, excessive coat, and eyelid abnormalities.

Other examples of disease phenotypes that are caused by selected traits include: hydrocephalus or syringomyelia in breeds with dome-shaped skulls, scoliosis in breeds selected for screw tail (caudal hemivertebral), and spina bifida in Manx cats.

Disease phenotypes that are linked to selected traits include; deafness due to the piebald or merle skin pigmentation genes, dermoid sinus associated with selection for the dermal ridge in Ridgeback breeds, cranio-facial defect in Burmese cats selected for a round head-type, abnormal uric acid (purine) metabolism linked to the desired spotting pattern in the Dalmatian breed, and osteochondrodysplasia in Scottish Fold cats associated with the cartilage defect causing the folded ears. It is important that breed standards and selection practices specifically avoid selection for extreme phenotypes and disease liability. Breed genetic health should be judged not on statistics of inbreeding coefficients or homozygosity, but on breed health surveys that accurately document the frequency of genetic disease.

GENETIC DISORDERS IN MIXED BREED DOGS & CATS
The most common genetic disorders seen across dog or cat breeds are also seen in the mixed or random-bred population. These are due to evolutionarily ancient disease-liability genes that
preceded the separation of breeds. In a five-year study of cases seen at the University of California-Davis veterinary medical teaching hospital, it was found that the prevalence of 13 of 24 common inherited disorders did not vary between purebred and mixed breed dogs. These included; hip dysplasia, patellar luxation, hypoadrenocorticism, the common hereditary cancers (hemangiosarcoma, lymphoma, mast cell tumor, and osteosarcoma), hypertrophic cardiomyopathy, mitral valve dysplasia, patent ductus arteriosus, ventricular septal defect, hyperadrenocorticism, and lens luxation. The disorders where purebreds were more common than mixed breed dogs were the more breed-specific disorders or those where (pre-breeding) diagnostic screening practices differed between the two groups. Mixed breed dogs had a higher incidence of cruciate ligament rupture and the control category of being hit by cars.

In a further study on these data, it was found that in 7 of the 10 genetic disorders where there was a prevalence difference between purebred and mixed breed populations, it was only a subpopulation of purebred groups that differed, based on disorders linked to common ancestry or common structural morphology. The majority of purebred groups did not differ from the mixed bred population in prevalence of the common disorders.

According to the AKC Canine Health Foundation the most common hereditary disorders occurring across all dogs include; hip dysplasia, epilepsy, hypothyroidism, allergies, inherited cancers (hemangiosarcoma, lymphoma, mast cell tumor, and osteosarcoma), patella luxation, cataracts, bloat, progressive retinal atrophy, elbow dysplasia, Legg-Calve-Perthes disease, inflammatory bowel disease, deafness, and liver shunts.

These results are reflected in what we seen in clinical practice. There is no difference genetically between an old purebred dog with bilateral hip arthritis and an old mixed breed dog with bilateral hip arthritis. They both have hip dysplasia. The purebred dog may have received the label at 2 years of age due to a hip radiograph, but the disease process is the same.

Autoimmune thyroiditis is the cause of primary hypothyroidism in dogs. Based on thyroid profiles run at the Michigan State University DCPAH, 10.7% of 55,053 mixed breed dogs tested affected for autoimmune thyroiditis. The average frequency of affected in purebred dogs is 7.5%. This does not mean that mixed breed dogs are more prone to autoimmune thyroiditis. They are more likely being tested due to clinical signs, while a percentage of purebred dogs are undergoing pre-breeding screening. However, these results show us that this hereditary disorder is seen frequently in both purebred and mixed breed dogs.

The most common feline hereditary diseases we see in practice are feline lower urinary tract disease (FLUTD or FUS), and inflammatory cystitis. As random-bred cats are our most frequent patients, it is no surprise that they represent the majority of affected cats. Feline diabetes is seen most frequently in mixed breed cats, though some breeds have an increased prevalence. Autosomal dominant polycystic kidney disease (PKD) is also occasionally seen in clinical practice in mixed breed cats with Persian or Himalayan ancestry.

**GENETIC DISORDERS IN DESIGNER BREEDS**

Around 10 to 15 years ago, there was a significant increase of designer breeds primarily sold through pet stores. These are first generation offspring from planned crosses between two breeds. This was due to the public perception of the poor genetic health of purebred dogs, and the genetic health advantage of cross-bred dogs. Designer breeds include Puggles, Yorkipoos,
Maltipoos, Cavishons, the more established Cockapoos, and others. In addition, new breed crosses were established that attempted to produce dogs that bred true, including Labradoodles and Goldendoodles.

Now that we have seen these designer crosses for their lifetimes, we see that they do not lack in their presentation with genetic disease. They are seen with the common genetic disorders such as allergies, hip dysplasia, cataracts, patella luxation, bloat, hypothyroidism, and others. In addition, some of these crosses are seen with morphological disease from the crossing of body types that were not developed to be bred together. The most frequent clinical result of this is dental disease, including issues with eruption, occlusion, crowding, and misplaced teeth.

A study of eye disorders in Labradoodles conducted in the UK showed that they suffer from multifocal retinal dysplasia (4.6%), cataracts (3.7%), and persistent pupillary membranes (1.4%). Labradoodles are also being diagnosed with hip dysplasia, elbow dysplasia, and inherited Addison’s disease; all recognized disorders in both parent breeds. Dogs affected with prcd-PRA (who must receive the recessive defective gene from both parents) are observed in Labradoodles, Goldendoodles and Cockapoos (Cocker Spaniel x Poodle crosses).

**IMPROVING THE GENETIC HEALTH OF DOGS & CATS**

From the above data, it is apparent that genetic disease in dogs and cats is due to the inheritance of disease liability genes. There is not much that we can do about genetic transmission of disease in randomly bred mixed breed dogs and cats, but for purposely bred (purebred and designer bred) animals, breeders must use due diligence to prevent inherited disease.

Some advocates of dog and cat breeding call for organized outbreeding programs that mate the least related individuals to each other to “rescue” breeds. These mirror the Species Survival Plans (SSP) formulated for rare and endangered species. Genetic diversity involves breeding representatives from diverse areas of the gene pool, but not necessarily the types of matings (outbreeding versus linebreeding) that they are involved in. **Outbreeding will not diminish the expression of breed-related genetic disease, as the causative genes are already dispersed in the population.** They will continue to produce affected individuals in a random fashion, which is what we see with the common genetic diseases in random-bred domestic cats and dogs.

When breeds show high frequency of genetic disease, or significantly diminished fertility and fecundity, they could have too high a genetic load of disease liability genes. In extreme instances they may require; a SSP-type plan, opening the stud book to importation, or cross-breeding to other related breeds. However, most breeds do not find themselves in such dire circumstances, and only require proper selection to improve their gene pools and genetic health.

Some studies bemoan the homozygosity found in breeds, and call for programs to increase minor allele frequencies. However, it is just as likely that genetic selection for quality and against undesirable traits is what reduced the frequency of these minor alleles in the first place. Blindly selecting for them without knowing their effect could significantly reverse selection-based breed improvement. This has been shown in cattle breeds.
Some call for programs to increase within breed diversity of major histocompatibility complex (MHC) haplotypes to improve the immune system of breeds. In no breeds has general limited diversity or random homozygosity of MHC haplotypes been shown to impair an individual’s immunity. The association with immune-related disease has to do with specific disease-related haplotypes inherited from the parent, and not necessarily the homozygosity of any random haplotype. Some disease-associated MHC haplotypes require homozygosity, and some require only one copy of the haplotype to confer disease risk. Other immune-mediated diseases are linked to specific genes outside the MHC complex. This again points to selection against disease liability genes as the most important factor in improving genetic health.

Most cat and dog breeds show adequate diversity and do not show signs of genetic depletion requiring rescue protocols. Breed maintenance requires;
- A large or expanding breed population
- Avoidance of the popular sire syndrome
- Avoidance of extreme phenotypes that can produce disease liability
- Monitoring of health issues in the breed
- Constant selection for quality and health

Responsible breeders perform genetic testing of parent breeding stock for breed-susceptible disorders. Official test results should be made available to prospective breeders, and to the pet and breeding-stock purchasing public. This is facilitated through open genetic health databases. It doesn’t matter whether a breeder is a large commercial breeder, or only breeds once. It is no longer acceptable to say that genetic disease “just happens.” In today’s environment, not testing for documented breed-related hereditary diseases is irresponsible and unethical breeding.

REFERENCES