Beagle breeders have long recognized the value of using health screenings and genetic testing to improve the health of the breed. Thus, in 2004, the National Beagle Club (NBC) joined the Orthopedic Foundation for Animals’ Canine Health Information Center (CHIC) program — only three years after it was founded.

Currently, the CHIC program lists 10 health tests for Beagle, as recommended by NBC. Four of the 10 health tests are DNA tests for genetic conditions that tell breeders whether an individual Beagle is a carrier, clear or affected. Breeders can use this information to help evaluate breeding pairs to selectively breed dogs. Selective breeding ultimately can be used to help reduce disease prevalence.

Of the four genetic tests, the one for Musladin-Lueke syndrome (MLS) is required to earn CHIC health certification. The other tests are optional but recommended. This includes testing for Lafora epilepsy, factor VII (FVII) deficiency, and neonatal cerebellar cortical degeneration (NCDD).

“Breeders who step up to the plate to health test their dogs and then openly allow others to see the results of their dogs’ health tests are helping to better the breed,” says Darlene Stewart, chair of the NBC Health and Genetics Committee.

**MLS: A REQUIRED HEALTH TEST**

When Musladin-Lueke syndrome was first reported in the 1970s in Beagles in the U.K. and Australia, the incidence rate was believed to be around 2 to 3 percent. The mysterious condition caused a variety of clinical signs, though dogs having the phenotypical characteristics of a broad skull with wide-set, slanted eyes and tiptoe walking were initially linked to the syndrome.

Nearly 40 years later, a genetic study began at the University of California-
Davis led by Mark W. Neff, PhD, using the foundation work started by Beagle breeders Judith M. Musladin, MD, Anton C. Musladin, MD, and Ada T. Lueke. Dr. Neff discovered a missense founder mutation in the ADAMTSL2 gene and appropriately named the disorder Musladin-Lueke syndrome in their honor.

“The MLS mutation probably originated in the 1830s when the modern Beagle breed was being developed in Great Britain, as it is broadly distributed in dogs around the world,” says Dr. Neff.

The Musladins and Lueke started collecting pedigrees and case information on this type of Beagle in the early 1990s and described the disorder in their 1998 book, “The New Beagle.” They believed that MLS had an autosomal recessive inheritance, which proved to be true.

Beagle breeder Bev Davies-Fraser of Red Deer, Alberta, Canada, contributed DNA from several Beagles out of her Waskasoo bloodline to aid the research. “A request was posted on a Beagle email list searching for dogs with clinical signs that included tiptoe walking and wide-set eyes,” she says. “A female puppy out of my first litter whelped in 1992 walked on her toes. At the time, I didn’t think too much about it because my foundation sire did the same thing.”

In 2004, Davies-Fraser was mentoring a new Beagle breeder who had bred to a descendant of her foundation sire when she recognized the disorder in the 3-week-old puppies. “I knew right away these puppies had the unusual syndrome because of their eyes,” she says. “I had the littermates to the dog my friend bred to, so I sent in DNA on these dogs and as many related dogs as I could along with their pedigrees, pictures and detailed descriptions,” says Davies-Fraser.

Likewise, Beagle owner Geraldine Aikman of Kennebunk, Maine, contributed DNA from her male Beagle “Jake.” “From the beginning when I got Jake at 6 months old, he had difficulty standing and would slip on wood floors,” she says. “When he laid down, his legs stuck out stiffly. He ran with a rocking gait, and his ears had a crease toward the back of the flap. He had a high-pitched bark and never bayed. He had seizures his entire life, and this is what caused his death at age 14.”

The University of California-Davis researchers used genome-wide association to identify the gene variant in Beagles for the connective tissue disorder that causes extensive fibrosis of the skin and joints. A more severe form of the disorder, geleophysic dysplasia, occurs in humans due to a mutation at the same gene locus. The DNA test for MLS in Beagles has been available since around 2010.

**LAFORA EPILEPSY: AN OPTIONAL BUT RECOMMENDED HEALTH TEST**

One of the most severe forms of canine epilepsy, Lafora disease is a late-onset progressive myoclonic epilepsy occurring around 7 years of age often after dogs have been bred. Beagles, Miniature Wirehaired Dachshunds and Basset Hounds share the same mutation, a variable expansion of a dodecamer repeat sequence in the NHLRC1 (EPM2B) gene.

The autosomal recessive disorder results in near-absent expression and loss of function of the gene. Affected dogs are not able to make glycogen into the soluble, spherical form that can be stored in the cells and used by the brain for energy. Instead, insoluble

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**SIGNS OF MUSLADIN-LUEKE SYNDROME**

- Short stature
- Thick, taut skin
- Stiff limbs and inability to perform full range of motion
- Short outer toes
- Severely restricted joint mobility
- Broad skull with wide-set, slanted eyes
- Creased ears
- Tiptoe gait
- Happy, pleasant temperament
- High-pitched bark
- Cardiac disease and seizures in some dogs
- Affected puppies have stunted growth, failure to thrive and bouts of pain
- Condition stabilizes when dogs are 1 year of age, with most having a normal life span unless there are other congenital defects
glycogen accumulates within cells into large clumps called Lafora bodies. When these cells accumulate in nerve cells, the nerve cells malfunction and degenerate, causing neural problems that lead to seizures. A dog diagnosed with Lafora epilepsy may live to 10 to 14 years of age despite having the disease.

Lafora disease was first recognized in Miniature Wirehairs in the U.K. more than three decades ago. Researchers in the U.K. sent pedigree information and DNA from affected dogs to Berge A. Minassian, MD, formerly of The Hospital for Sick Children at the University of Toronto in Canada, who was studying a similar inherited, severe form of progressive myoclonic epilepsy in humans that occurs in late childhood or adolescence.

Dr. Minassian identified the EPM2B gene mutation for Lafora disease in Mini Wirehairs in 2005. The gene variant disables the gene from controlling laforin and from protecting tissues against carbohydrate accumulation. As the Lafora bodies accumulate, they have a neurotoxic effect in the central nervous system. When Lafora bodies amass within the nerve cells of the brain, the cells start to malfunction and degenerate causing twitching, jerking and sometimes seizures.

As the disease progresses, dogs experience other neurological problems, including dementia and difficulty walking. Besides brain tissue, Lafora bodies are found in muscles, skin, liver, and the heart. Lafora disease is a progressive myoclonic epilepsy and a glycogen metabolism disorder. The DNA test for Lafora epilepsy became available in 2017 for Beagles.

**FACTOR VII DEFICIENCY: AN OPTIONAL BUT RECOMMENDED HEALTH TEST**

Factor VII (FVII) deficiency, which can cause mild-to-moderate bleeding, was initially recognized in a colony of research Beagles. Investigators at the University of Pennsylvania School of Veterinary Medicine identified in 2006 the single missense G96E mutation in canine chromosome 22 that accounts for the autosomal recessive disorder.

FVII is a vitamin K-dependent glycoprotein synthesized in the liver and secreted into the circulation that has a pivotal role in the initiation of coagulation. A similar FVII deficiency occurs in humans, also causing mild-to-severe bleeding. In Beagles, the disorder has since been found to occur in companion dogs as well as research dogs.

“Reports of Beagles with FVII having bleeding issues are infrequent,” says Stewart of the NBC Health and Genetics Committee. “Many affected Beagles undergo surgery, dental cleanings and even cesarean sections without abnormal bleeding. Owners should be aware of their dog’s Factor VII status and should inform their veterinarian,

**SIGNS OF LAFORA EPILEPSY**

- Myoclonus, or sudden twitches or jerks of the neck and limb, that are spontaneous or a reflex action triggered by sudden noise, bright light, sudden movement, or flickering visual stimuli
- Hypnic jerks, the type of sudden jerk people experience as they fall asleep
- Generalized tonic-clonic seizures involving stiffening and twitching of the muscles
- Less common signs include focal seizures characterized by jaw smacking, fly catching or panic attacks
- Later signs include dementia, blindness, aggression to people and dogs, deafness, and fecal and urinary incontinence due to loss of housetraining
A BALANCED APPROACH TO BREEDING BEAGLES

Taking breeding advice from the “Review of the Current State of Genetic Testing in Dogs” helps put in perspective how to breed healthy dogs with quality traits when inherited diseases crop up in bloodlines.

“Beagle breeders must balance their choices to produce the fewest affected animals while removing the fewest animals from the gene pool to avoid a loss of genetic diversity,” says manuscript co-author Anita Oberbauer, PhD, professor at the University of California-Davis. “When selecting mating pairs, you should think about the characteristics of individual dogs and the puppies you hope to produce but also consider how you can make choices to improve the breed as a whole for future generations.”

Below are key learnings taken from this paper that apply to genetic testing of Beagles.

• Some genetic tests are breed-specific, such as those for Musladin-Lueke syndrome (MLS), factor VII (FVII) deficiency, Lafora epilepsy, and neonatal cerebellar cortical degeneration (NCCD) in Beagles. Breed-specific tests are not universally relevant or applicable across all dogs and dog breeds.

• Large-scale panel genetic testing, also known as multiplex testing, looks at the presence of variants for many, sometimes hundreds, of different traits. These reports tend to inform dog breeders and owners of mutations and disorders that are not relevant in their dog since a specific genetic background may be necessary for that mutation to cause disease. If a disease mutation that typically occurs in a different breed is part of your Beagle’s panel genetic testing report, these findings should be interpreted cautiously.

• To preserve genetic diversity, a quality dog tested as a carrier can be bred to a clear dog free of the mutation. Fifty percent of puppies would be clear and also have the genetic richness of the carrier parent. Clear puppies from this breeding could be used in the next generation.

• Insightful knowledge from genetic testing about the likelihood of a dog to develop a hereditary disease is particularly meaningful for disorders that develop later in life, such as Lafora disease, and for which clinical surveillance and/or lifestyle or dietary modifications could improve the dog’s quality of life. Proper interpretation of genetic tests is fundamental to avoid misapplication and negatively impact genetic variability.

• Breeders should gradually apply selection based on genetic testing to improve breed health. Most importantly, breeders should not depopulate the breed and cause a genetic bottleneck from loss of genetic diversity. Always be mindful of how your choices impact the population of the Beagle breed as a whole.
Purina appreciates the support of the National Beagle Club, particularly Darlene Stewart, chair of the Health and Genetics Committee, for helping us to identify this topic for the Beagle Update.

Genome-wide mRNA sequencing — the first time this sequencing application was used to identify a candidate gene — was performed on the puppy’s DNA. Then, genotype analysis was done on the sire, dam, 10 clinically unaffected littermates, and the male puppy from the 2007 litter.

The discovery of an 8 bp deletion in the beta-III spectrin (SPTBN2) gene was found to cause the condition, now known as neonatal cerebellar cortical degeneration (NCCD). Humans have a similar condition involving three mutations in the SPTBN2 gene that is associated with the autosomal dominant condition spinocerebellar type 5 (SCA5). Beta-III spectrin is critical for Purkinje cell development, and an absence of this protein can lead to cell damage and the neurological dysfunction seen in the Beagle puppies. The DNA test to identify a Beagle’s inheritance of NCCD has been available since around 2012.

A rare disease, NCCD causes degeneration of cells in the brain’s cerebellum that are responsible for coordinated movement. As early as 2 to 3 weeks of age, the incoordination is noticeable. After a few weeks, the condition levels off. Affected dogs can live a normal life span, though they will have serious mobility issues throughout their lives.

**HEALTH TESTING SUCCESS**

Just as the National Beagle Club envisioned in 2004 when the parent club joined CHIC, health testing pays off when breeders use these tests as a tool to make selective breeding decisions and advance their breeding programs.

“Today, you seldom hear about dogs with MLS,” says Davies-Fraser, whose foundation sire was a carrier. “The more breeders use these tests to screen their breeding partners, the better results we will get for the breed as a whole.”

Stewart agrees. “As more genetic tests are developed, breeders should use them knowledgeably to advance their bloodline and the breed,” she says. “It takes all of us working together to ensure a healthy future for our beloved Beagles.”

**SIGNS OF NEONATAL CEREBELLAR CORTICAL DEGENERATION**

- Incoordination
- Wide-based gait causing clumsy, staggering movements
- Loss of balance
- Inability to regulate range of movement
- Tremors

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CHIC HEALTH TESTING REQUIREMENTS FOR BEAGLES*

Required Health Tests
- **Hip Dysplasia** using OFA or PennHip evaluation
- **Eye Examination** by a board-certified veterinary ophthalmologist
- **Musladin-Lueke Syndrome** using a DNA-based test from an approved laboratory, with results registered with OFA, and with first-generation offspring of tested dogs eligible for clear by parentage
- **Cardiac Evaluation** based on a congenital, basic or advanced cardiac examination
- **Autoimmune Thyroiditis** using OFA evaluation done at minimum age of 24 months

Optional But Recommended Health Tests
- **Advanced Cardiac Evaluation** performed by a board-certified veterinary cardiologist
- **Patellar Luxation** using an OFA evaluation done at minimum age of 1 year
- **Lafora Epilepsy** using a DNA test from an approved laboratory, with results registered with OFA
- **Factor VII Deficiency** using a DNA test from an approved laboratory, with results registered with OFA
- **Neonatal Cerebellar Cortical Degeneration** using a DNA test from an accepted laboratory, with results registered with OFA

*The Orthopedic Foundation for Animals, working with the National Beagle Club, recommends these basic health screening tests for all breeding stock. Dogs meeting these basic health screening requirements will be issued Canine Health Information Center (CHIC) numbers. Note that for CHIC certification, a dog’s testing results do not need to be normal but must be made public so that responsible breeders can make informed breeding decisions. In addition to those health requirements, a dog must be permanently identified via a microchip or tattoo to qualify for a CHIC number.
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