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REVIEW

CLINICAL SPOTLIGHT

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GENETIC TESTING
Practical dos and don'ts for cats

Leslie A Lyons

Introduction

'It's in our DNA!' This slogan suggests something is 'natural' to one's being or one's behavior. Whether it is a discussion about healthcare or a company implying innovation and quality are part of their core mission and values, 'It's in our DNA' suggests quality and accuracy. Genetic testing of DNA variants (mutations) that cause diseases and traits are generally conducted using assays with high degrees of sensitivity and specificity and thus, indeed, produce data with high quality and accuracy. However, the suggested usage and interpretation of genetic data and how the results are presented by commercial laboratories may be confusing for veterinary practitioners and owners, leading to misinterpretations for healthcare, improper genetic counseling, and poor breed and population management. For instance, the default recommendation from many veterinarians has been to neuter cats with heritable diseases, which could potentially be considered malpractice, as the entire cattery and/or population need to be considered to maintain genetic diversity and to not eliminate many favorable qualities and characteristics of a cat. In addition, many laboratories now offer large panels of genetic tests, which can result in cat owners attending a veterinary appointment with a long list of DNA test results. However, many of the genetic tests are not appropriate for every breed and many are not appropriate for any cat at all. Veterinarians therefore need to understand and be confident with interpreting the results to be able to suggest appropriate healthcare and mating practices.

The information provided in this review will help veterinarians understand the genetic tests that should be requested, explains the best places to obtain genetic services and suggests recommendations for breed management based on test results. The practical tips – dos and don'ts – of genetic test usage in veterinary healthcare are also discussed.

The presentation of genetic data and its suggested usage and interpretation may be confusing, leading to misinterpretations for heathcare, improper genetic counseling, and poor breed and population management.

Practical relevance: A significant number of genetic variants are known for domestic cats and their breeds. Several DNA variants are causal for inherited diseases and most of the variants for phenotypic traits have been discovered. Genetic testing for these variants can support breeding decisions for both health and aesthetics. Genetic testing can also be used to monitor for the health of, or provide targeted therapy for, an individual cat and, more widely, can progress scientific discovery. Technological improvements have led to the development of large panel genetic testing, which can provide many DNA results for a low cost.

Clinical challenges: With the development of large panel genetic testing has come companies that can carry out this service, but which company is best to use may not always be clear – more tests are not necessarily better. Usage and interpretation of genetic data and how the results are presented by commercial laboratories may also be confusing for veterinary practitioners and owners, leading to misinterpretations for healthcare, improper genetic counseling, and poor breed and population management.

Evidence base: The information provided in this review draws on scientific articles reporting the discovery, and discussing the meaning and implications, of DNA variants, as well as information from the Online Mendelian Inheritance in Animals (OMIA) website, which documents all the DNA variant discoveries. The author also provides suggestions and recommendations based on her personal experience and expertise in feline genetics.

Audience: This review is aimed at general practitioners and discusses the genetic tests that can be performed, what to consider when choosing a testing laboratory and provides genetic testing counseling advice. Practitioners with a high proportion of cat breeder clientele will especially benefit from this review and all veterinarians should realize that genetic testing and genomic medicine should be part of diagnostic plans and healthcare for their cat clients.

Keywords: Genetic testing; genetic counseling; genetic service providers; Online Mendelian Inheritance in Animals; OMIA

Leslie A Lyons
PhD
Veterinary Medicine and Surgery,
College of Veterinary Medicine,
University of Missouri, Columbia,
MO 65211, USA

Email: lyonsla@missouri.edu

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A DNA sequence by any other name

Mammals have approximately 2.5 gigabases (Gb) of DNA, which is a variable sequence of only four nucleotides – cytosine (C), adenine (A), thymine (T) and guanine (G). A cat has 18 autosomes and the XY sex chromosomes. Each autosome has a maternal and paternal copy, thus the 38 cat chromosomes (2 × 18 + X + Y) are composed of 38 long strings of DNA, which are in each cell of the body except the red blood cells of many species. Approximately 21,000 genes are distributed along these chromosomes and each gene has slight differences in the nucleotide sequences between the maternal and paternal copies of the same chromosome (ie, alleles). The DNA differences are also known as 'variants' and these are caused by the mechanism of mutation. Historically, DNA variants were termed 'mutations', which can have negative connotations; however, all organisms need mutations to produce new genetic variation and new alleles! Some mutations are good, some are bad and most are neutral, which cause no changes to the protein produced by the gene nor affect the gene's regulation. When DNA variants have a frequency of over 1% in the population, they are considered polymorphic. Thus, variants are also known as single nucleotide polymorphism/variants (SNPs/SNVs), when the variant is only one or a couple of nucleotide changes, or structural variants (SVs), which are more complex DNA changes.

Which variants can be genetically tested in domestic cats?

The Online Mendelian Inheritance in Animals (OMIA) website (www.omia.org) documents all the DNA variant discoveries for cats as well as many other species.[1,2] Everything a veterinarian needs to know when investigating feline genetic tests can be found on the OMIA website, including information regarding the DNA variant, in which breed the variant was discovered, and all the original scientific articles documenting the discovery and discussing the meaning and implications of the variant, as well as the clinical aspects of the disease or trait.

Currently, 197 genetic variants are known for cats (Table 1), including all the different causal variants for inherited diseases and phenotypic traits (see 'Testing all causal DNA variants' box). There are approximately 45 phenotypic variants, with some of these being found in many different breeds and some being specific to certain cat breeds. Approximately 140 DNA variants are associated with diseases, blood type or other conditions ('phene' in OMIA).

While genetic testing will determine the presence or absence of a particular DNA variant, unidentified, modifier DNA variants in the genetic background of a cat can alter the presentation of traits and diseases, explaining incomplete penetrance of a disease (where a disease may not present in an individual's lifetime), different ages of onset and overall variable expression of diseases. When breeding cats, this means that 'good lines' can suddenly become 'bad lines' without warning as likely other, unknown genetic variants alter the disease severity.

As discussed, many variants can be genetically tested in cats, but which genetic tests are important for veterinary healthcare and why? And when and why would these tests be used?

Table 1 Classifications of 197 cat DNA variants documented in OMIA

Variant type	Number of genes (106)	Number of alleles (197)	Gene (number of variants, trait locus name)
Felid-specific*‡	2	2	*TAS1R2*; *UGT1A6*
Cancer driver†‡	2	2	*STAT5B*; *EXT1*
VUS/modifiers‡	4	6	*ALMS1*; *ARSB* (mild); *F12* (2); *TPO* (2)
Blood group	1	14§	*CMAH*
Wellness	3	4	*MDR1*; *F9* (2); *F11*
Phenotypes and traits	16	46	See OMIA
Breed trait disorder	7	14	*ALX1*; *KIT* (*W*); *LMBR1* (3, *Pd*); *PAX3* (3, *DBE*); *TBX1* (4, Mx); *TRPV4* (*Fd*); *UGDH* (*Dw*)
Breed disorders	35	44	See OMIA
Random-bred disorders	48	65	See OMIA

*_TAS1R2_ and _UGT1A6_ are found in all felids, making cats different from other species
†The variants found in cancer types (_STAT5B_ and _EXT1_) are found in the tumors and will not be present in the normal DNA of the cat
‡Felid-specific, cancer drivers and variants of unknown significance (VUS) should not be used for breeding decisions
§The association of several variants in _CMAH_ for the cat blood group are debated
OMIA = Online Mendelian Inheritance in Animals (www.OMIA.org)

The Online Mendelian Inheritance in Animals (OMIA) website provides all the information a veterinarian needs to know when investigating feline genetic tests.

Testing all causal DNA variants

Many diseases and phenotypic traits have more than one causal DNA variant in the same gene, or perhaps variants in a different gene, that result in nearly the same clinical condition. A list of all the DNA variants for any given disease or phenotype can be created for the cat by sorting the OMIA list by the 'variant phenotype' and/or 'gene' columns.

When genetic testing is going to be performed for a patient, the OMIA variant list should be compared with the offerings of the selected service laboratory to confirm that all variants for the disease or phenotype are being tested. If not all OMIA DNA variants are listed by the company, then more than one genetic service, or a more comprehensive service, may be required.

Routine genetic testing for diseases in cat breeds

Approximately 127 DNA variants in cats cause diseases and health problems. However, only 44 (~35% of all disease-causing variants and ~22% of all 197 variants) disease variants are important to cat breeders and should be closely monitored for health. Table 2 presents the diseases found in specific cat breeds. If a patient represents a specific breed, the breed-associated disease tests are highly recommended for routine genetic testing to predict healthcare, to know which health concerns to monitor and to establish safe breeding practices. The approximately 69 disease-causing DNA variants that are not important for cat breeders were discovered in random-bred (domestic, moggy, house, barn, alley) cats, or within a research colony of cats, and, therefore, are very unlikely to be identified again or become established within cat breeds. These variants are extremely rare, if not particular to an individual cat, aka private DNA variants, that may never be identified again. General population screening for disease variants that were originally identified in random-bred cats has a very low rate of re-identification. However, if a particular disease is suspected, testing for all known variants in the patient is prudent (see 'Genetic testing for a suspected heritable disease' box), even if the discoveries had previously been found in random-bred cats.

Genetic testing for a suspected heritable disease

If any cat, whether one representing a breed or a randomly bred population, has a suspected heritable disease, such as porphyria, cystinuria and hypertrophic cardiomyopathy (HCM), or a suspected inborn error of metabolism, genetic testing for the known variants for the suspected disease can be performed to help determine the cause and potentially identify gene-related treatments (ie, precision/genomic medicine). If the genetic test for a suspected heritable disease is positive, the disease can be better managed and targeted therapies may potentially be available. However, if genetic testing is negative, additional genetic studies will be required to find the causal variant for this new, undefined condition. The identification of new DNA variants has become vastly less expensive and easier to accomplish with massively parallel sequencing techniques called whole genome sequencing (WGS) and whole exome sequencing (WES) (see 'Large panel genetic testing' box later).[3,4]

Table 2 Diseases to be monitored in specific cat breeds*

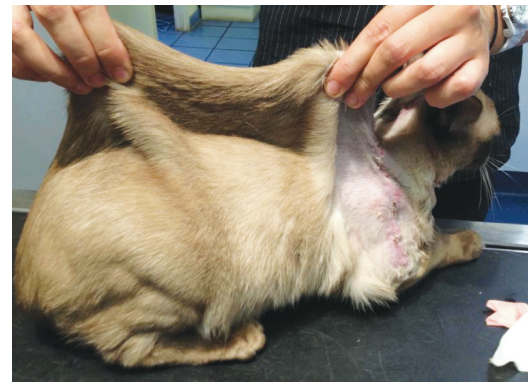
Breed*	Genes† (AD = dominant; X = X-linked)	Diseases
Abyssinian, Somali	*CRX*‡ (AD), *CEP290*§, *PKLR*§¶	Blindness, blindness, pyruvate kinase deficiency
American Shorthair	*PKD1* (AD), *ALX1*	Polycystic kidney disease, craniofacial defect
Asian, Australian Mist, Burmese, Burmilla, Bombay, Singapura	*ALX1*, *CLCN1*, *COL5A1*, *HEXB*, *WNK4*	Craniofacial defect, myotonia congenita, EDS, gangliosidosis, hypokalemia
Bengal	*COL5A1*, *CEP290*§, *KIF3B*, *PKLR*§¶	EDS, blindness, blindness, pyruvate kinase deficiency
Birman	*FOXN1*	Hypotrichosis (hair loss) with shortened lifespan
British Shorthair	*FASLG*, *LTBP3*	Autoimmune lymphoproliferative syndrome, skeletal dysplasia
Devon Rex, Selkirk Rex, Sphynx	*COLQ*, *SLC7A9*	Spasticity, cystinuria
Donskoy	*HPS5*	Pink-eye
Korat	*GLB1*, *HEXB*	Gangliosidosis 1 and gangliosidosis 2
Norwegian Forest Cat	*GBE1*	Glycogen storage disease IV
Maine Coon (also polydactyl)	*DMD* (X), *F11*∞, *LIX1*, *MTM1* (X), *MYBPC3* (AD), *SLC7A9*	Muscular dystrophy, bleeding, spinal muscular atrophy, myotubular myopathy, HCM, cystinuria
Persian, Exotic, Scottish Fold, Himalayan, Selkirk Rex	*AIPL1*, *LYST*‡, *MAN2B1*, *PKD1* (AD)	Blindness, Chediak–Higashi syndrome, alpha-mannosidosis, polycystic kidney disease
Ragdoll	*MYBPC3* (*AD*)	HCM
Oriental, Siamese, Colorpoint, Peterbald	*ARSB*#, *CEP290*§, *GLB1*, *HMBS*, *LTBP2*, *NPC2*, *PKLR*§¶, *SLC7A9*	MPS IV, blindness, gangliosidosis 1, porphyria, glaucoma, Niemann–Pick C2, pyruvate kinase deficiency, cystinuria
Russian Blue	*TPO*	Hypothyroidism
Siberian	*PKD2*	Polycystic kidney disease
Toyger	*GDF7*	Holoprosencephaly
Turkish Van	*SLC39A4*	Acrodermatitis enteropathica

*Long- or shorthaired varieties of the breeds are not listed. This breed list may vary from the Online Mendelian Inheitance in Animals (OMIA) list as the segregation of the variant within some breeds is not well established
†All diseases are autosomal recessive unless otherwise noted
‡*CRX* blindness and the *LYST* Chediak–Higashi syndrome variants are likely eradicated from their breeds
§*CEP290* and *PKLR* variants have spread to various breeds and increased in frequency. The number of breeds with these variants has expanded and these variants should potentially be monitored in all breeds
¶Disease association for *PKLR* has not been established in all cat breeds
∞Test for *F11* if the cat needs surgery – be sure to monitor
Breeders should work to eradicate the disease variants from their breeding lines, except #*ARSB* (mucopolysaccharidosis [MPS] IV), which includes the mild modifier variant – monitor, as other MPS variants must be present to cause disease
EDS = Ehlers–Danlos syndrome; HCM = hypertrophic cardiomyopathy

Many of the diseases found in breeds are either congenital or have an early onset, and have a very poor prognosis with a shortened lifespan. The majority of diseases also have very low allele frequencies in the population and thus, with widespread genetic testing and selective breeding, most, although not all, of the genetic diseases in cat breeds could be easily eradicated within a few years. With this in mind, the World Small Animal Veterinary Association Hereditary Disease Committee has formally requested the World Cat Congress and its member cat registries during their annual meeting (Tasmania, June 2023) to consider mandatory genetic testing for the specific diseases within each breed. Because the health conditions of many recessive traits have high morbidity, an early age of onset and result in a high level of mortality, cats affected with disease are generally not bred or not able to breed and should be neutered. One of the most important reasons for genetic testing is to identify cats that are carriers for recessive conditions. Overall, carriers for recessive diseases should not be bred to other carriers. In addition, any cats with recessive disease variants should be retired and replaced in the breeding program as quickly as feasible, keeping in mind that replacement must be balanced with maintaining genetic diversity as well as the other favorable qualities of the cat.

A few of the recessive traits are recognized later in a cat's life, such as the cutaneous asthenia variants (also known as Ehlers–Danlos syndrome; see Figure 1) in *COL5A1*[5] and cystinuria in *SLC7A9*.[6] Although rare, these variants may need to be monitored in a breed as they might be detected after a mating has already occurred, when the cat was not yet affected, and also because the resulting conditions are less well known by cat breeders. Hypokalemia, which is caused by a variant in the gene *WNK4*, can be identified when a cat is older and undergoes a stressful situation.[7] This disease can be treated with potassium supplementation; however, eradication of the variant is important to prevent the spread of the disease in the breed population.[8] Burmese breeders have actively attempted to eliminate this variant from the population and the current disease and variant frequencies are suspected to be very low.

Figure 1 **Cats with cutaneous asthenia can display with skin extensibility, as shown in this cat.** *Courtesy of Naomi Hansen*



Late-onset conditions are among the most difficult diseases to manage in breed populations, specifically the variant for HCM in Maine Coon cats.[9] HCM is a heterogeneous disease and even the Maine Coon breed population has more than one cause for HCM, but only one DNA variant is known, in the gene *MYBPC3*. Consequently, the HCM variants for Maine Coons and Ragdolls are considered risk factors because cats with either one or two copies of their respective HCM variants in *MYBPC3* could present with late-onset disease.[9,10] However, cats with the variant(s) might not present with HCM in their lifetime and thus the genetic test in Maine Coons is not 100% predictive for HCM. Cats homozygous for the known variant are more likely to have earlier onset disease; however, cats with one copy of the HCM variant in *MYBPC3* have still been known to have disease. Historically, the variant has had a high frequency in populations of Maine Coons – over 20%. Eradication of the variant therefore needs to be well managed so the allele frequency is reduced but without more inbreeding and more population bottlenecks, as these aspects of poor population management could lead to other diseases becoming more prevalent. General recommendations for traits with high frequencies are to, ideally, not mate two carriers, or to not overbreed with any one carrier and remove carriers from the breeding program with the next generation of offspring. Cats with positive HCM genetic tests need to be monitored via auscultation and echocardiograms for onset of cardiac disease.

Poor genetic monitoring and breeding practices have led to an increase and spread of some disease variants. The *CEP290* variant, which causes an autosomal recessive, late-onset blindness, and the pyruvate kinase deficiency variant (*PKLR*) have spread to many cat breeds.[11,12] Both variants were first identified in Abyssinian, Somali and Siamese cats but now Oriental Shorthairs are in dire need of appropriate genetic management as nearly 33% of a tested population indicated the presence of the *CEP290* variant.[13,14] Breeders may not have been breeding carrier to carrier but they did not remove carriers in

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Phenotypic traits are among the most important genetic tests for cat breeders and important for cattery management.

subsequent generations, or they overbred a particular cat (popular sire effect) that was a carrier of the variant, leading to the spread of the variant in the population. Because of the spread, most Asian-derived breeds should now be genetically tested for the *CEP290* and *PKLR* variants until each breed is established as clear and not at risk for the diseases or having carriers in the populations.

A success story for genetic management of a breed with a prevalent disease is Persians and the variant causing polycystic kidney disease (PKD). In 2004, when a test for this disease was released, many population studies conducted by ultrasound screening indicated that 20–38% of Persians worldwide had PKD.[15] Genetic testing has now indicated the frequency of the variant to be ~7% (University of California, Davis Veterinary Genetics Laboratory, personal communication);[14] with slow and continued elimination of PKD-positive cats from breeding programs, this disease could be eradicated from the Persian and related-breed populations.

Genetic testing for phenotypic traits

Approximately 60 phenotypic variants are found across different breeds or are specific to particular breeds. Phenotypic traits include coat colors, pattern types, fur types, ear fold, and leg and tail length. The current list of genetic tests available for the physical appearances of cats can be found in Table 3. Phenotypic traits tend to have the most presentations with multiple DNA variants within the same gene (alleles). Thus, a service laboratory should be selected that offers the most alleles for a trait, which can be determined by comparing the test offerings with the listings in OMIA to be certain all DNA variants are available and tested (see 'Testing all causal DNA variants' box). Phenotypic traits are among the most important genetic tests for cat breeders and veterinarians should be aware that these tests are important for cattery management.

Table 3 Phenotypes found in pedigreed and random-bred cats

Locus	Gene	Alleles	Variant presentation
Agouti, A	*ASIP*	A^{+}, *a*, A^{PB}	Solid, charcoal*
Brown, B	*TYRP1*	B^{+}, *b*, b^{l}	Brown, cinnamon coloration
Color, C	*TYR*	C^{+}, c^{m}, $c^{b} = c^{s}$, *c*, c^{a}	Temperature-sensitive color (Siamese, Burmese), mocha, full albinism
Dilute, D	*MLPH*	D^{+}, *d*	Uneven color distribution (dilution)
Extension, E	*MC1R*	E^{+}, *e*, e^{r}, e^{c}	Increased pheomelanin
Folded ear	*TRPV4*	***Fd***, fd^{+}	Scottish Fold ear
Glitter, Gltr	*FGFR2*	$Gltr^{+}$, *gltr*	Sheen in fur
Gloves	*KIT*	G^{+}, *g*	Gloves (Birman)
Hairless	*KRT71*	***Hr***, hr^{+}	Hairless (Sphynx)
Inhibitor, I	*Unknown*	***I***, i^{+}	No pheomelanin
Japanese, Kurilian Bobtail	*HES7*	***JBT***, jbt^{+}	Bobbed or kinked tail
Long, L	*FGF5*	*L*, l^{RAG}, l^{NFC}, l^{MCC}, *l*, l^{MCC2}	Long hair
Lykoi	*HR*	Hr^{+},hr^{TN}, hr^{CA}, hr^{Fr}, hr^{NC}, hr^{TX}, hr^{VA}	Absent undercoat
Orange, O	*Unknown*	X^{O}, X^{o+}	Color and pattern
Manx – tailless	*TBX1*	***Mx¹***, ***Mx²***, ***Mx³***, ***Mx⁴***, mx^{+}	No or short tail
Polydactyla	*LMBR1*	***Pd^{H}***, ***Pd^{UK1}***, ***Pd^{UK2}***, pd^{+}	Extra toes (Maine Coon)
Spotting	*KIT*	***S***, s^{+}	Bi-color (*Ss*), Van (*SS*) color – pattern
Rex (Cornish, German)	*LPAR6*	*R*, r^{+}	Curly coat
Rex (Devon)	*KRT71*	*Re*, re^{+}	Curly coat
Rex (Selkirk)	*KRT71*	***Rs***, rs^{+}	Curly coat
Rex (Ural)	*LIPH*	*Ru*, ru^{+}	Curly coat
Ticked, Ti	*DKK4*	ti^{+}, ***Ti^{A}***, ***Ti^{CK}***	Pattern, no pattern
Tabby, T	*LVRN*	T^{M+}, tb^{1}, tb^{2}, tb^{3}, tb^{as}	Blotched – classic
Variable wideband, VWB	*CORIN*	VWB^{+}, vwb^{SIB}, vwb^{eSIB}, vwb^{BSH}	Color and pattern
White	*KIT*	***W***, w^{+}	No pigmentation

The allele with a '+' sign is the normal, wild type allele, as defined by random-bred cats. Alleles with capital letters are the dominant allele and alleles with lower case letters are recessive. The equal sign '=' implies alleles that are codominant to other specific alleles and a difference in presentation is evident in the heterozygous cat. Codominance effects are not known for many alleles since the heterozygotes have never been documented.
Note – not all of the long- or shorthaired varieties of the breeds are listed. Bolded traits are autosomal dominant
*Charcoal presents when a cat has both a domestic cat non-agouti allele, *a*, and an allele from the leopard cat, A^{PB} (a/A^{PB})

Purely aesthetic phenotypic traits

Most, but not all, phenotypic traits are purely aesthetic attributes and do not pertain to feline health. The determination of the genetic variants for purely phenotypic (aesthetic) traits still leads to improved healthcare for the cat, however. If a veterinarian is working closely with a cat breeding program, these traits are important to determine the best mating practices to produce cats with the most desired phenotypes. Using genetic tests for cattery management leads to the production of cats with more value for both breeding and selling, thereby improving the income of the cattery, and lessening the financial and spatial requirements of cats that do not have the favored phenotypes. This would likely lead to fewer cats being bred and thus in the cattery, which, in turn, would typically result in fewer issues with stress and lower infectious disease burdens, thereby improving the wellbeing and health of the entire cattery. Breeders may also not be contributing as many cats to the overall domestic cat population.

Aesthetic phenotypic traits associated with health concerns

Several aesthetic phenotypic traits are associated with health concerns in domestic cats, and even define a specific breed; four of these traits (tailless, folded ears, dwarfism and polydactyla; see Figure 2) have genetic tests available.[16–21] While a genetic test is not usually required to show the presence of dominant traits, in some cases testing can still be useful (see the 'Do dominant phenotypic traits need to be genetically tested?' box).

The DNA variants causing taillessness often lead to lameness, incontinence and constipation in cats due to the disruption of the caudal and sacral vertebra and the associated innervations (also known as Manx syndrome).[26–29] Two copies of the Manx DNA variant are lethal in utero and thus live kittens with two copies are never born. However, as Manx cats have four possible variants for *Tailless* and a correlation between the variants and the presence of Manx syndrome has not yet been established, Manx/Cymric cats should be genetically tested to monitor which variant is present to help determine which cause health problems. Pain management should be considered in cats with any of the tailless variants at this time.

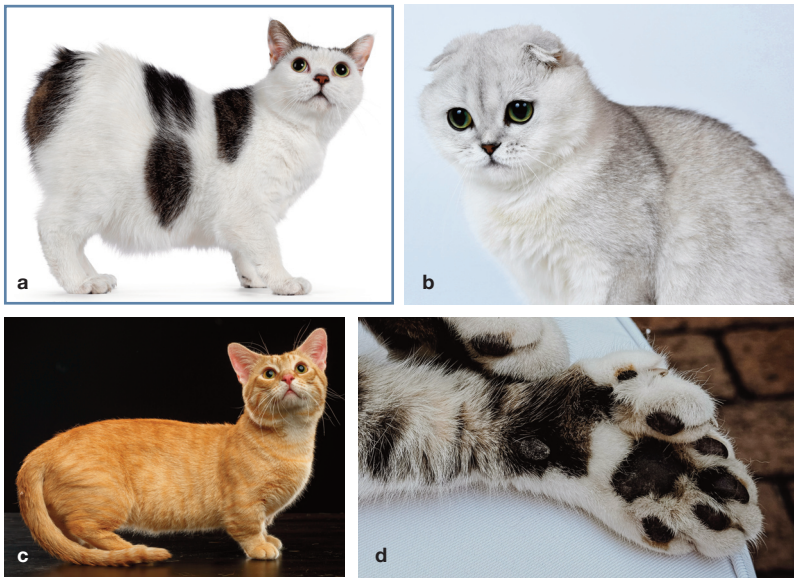

Figure 2 **Phenotypic traits associated with health concerns in domestic cats: (a) tailless (Manx); (b) folded ears (Scottish Fold); (c) dwarfism (Munchkin); and (d) polydactyla.** *Images by (a) Nynke via AdobeStock, (b) Sergey Semin via Unsplash, (c) TrapezaStudio via AdobeStock and (d) Zoey Li via Unsplash*

For a dominant trait, it may be useful to know which variant is present and/or if there are one or two copies of the variant present.

For the dominant variant causing the folded ears of the Scottish Fold breed, two copies of the DNA variant tends to cause a faster and more severe presentation of osteochondrodysplasia.[30–32] Cats with folded ears should therefore be tested to confirm if one or two copies of the variant is present. Typically, breeders have used the breeding scheme of mating affected (folded-eared) cats with normal (straight-eared) cats to produce cats with only one copy of the variant (similarly for taillessness, tailless cats are typically bred with long-tailed cats).

Do dominant phenotypic traits need to be genetically tested?

A dominant trait requires only one copy of the DNA variant to be present to manifest its expression; there are no 'carriers' for dominant traits. Thus, if a cat does not have the phenotype in question, there is usually no need for a genetic test. There are ten autosomal dominant traits (loci) (eg, folded ears,[16] tailless,[17] bobbed tail,[22] ticked coat pattern,[23] all white fur[24,25]) accounting for 16 variants (alleles) (Table 3) for which genetic testing is available but would not typically be needed if the cat is not displaying the affected phenotype. In some cases, however, dominant traits have been shown to have incomplete penetrance; thus, normal offspring from cats with dominant traits may need to be tested to verify an absence of the dominant trait.

Testing can also be useful to determine if there are one or two copies of a dominant variant; for instance, to help predict the extent of any health problems associated with the dominant variant (see the discussion of the folded ears variant in the 'Aesthetic phenotypic traits associated with health concerns' section as an example), investigate which variant causes health problems and improve the efficiency in breedings. For the last, for instance, a breeder might want to test a White Russian for the *Dominant White* variant (*W*) as cats with two copies will produce all-white offspring regardless of the other parent's coloration. In addition, where dominant traits have more than one variant, testing is recommended to determine which variant(s) is present.

However, like the tailless variants, the folded-ear variant is unpredictable and, sometimes, only one copy can lead to cats with severe osteochondrodysplasia. As for cats with a tailless variant, pain management should be considered in cats with the folded-ear variant.

Polydactyl cats[20,21,33] and dwarf cats[18,19] are also under scrutiny, but health concerns are less obvious than for cats with the tailless and folded-ear variants. A new breed termed the 'Munchkin' or 'Minuet' represents a form of disproportionate dwarfism in cats. In contrast to most disproportionate dog breeds being due to recessive DNA variants, only one dominant DNA variant causes the disproportionate dwarfism phenotype in cats. Like *Tailless*, two copies of the cat dwarfism DNA variant are lethal in utero, and thus live kittens with two copies are never born.[24] The gene associated with cat dwarfism is different from any dwarfism gene known in people or dogs, and can be evaluated to newly define undiagnosed human patients. In addition, since the cat dwarfism gene is different from the genes known in dogs,[34–36] cats likely do not have a risk for intervertebral disc ruptures. Although joint health has been examined in a few dwarf cats, long-term evaluations for osteoarthritis and joint pain should be carried out in these cats.[18] These variants will be less harmful if good breeding practices that consider the long-term health of the cat, such as minimal extra toes in polydactyl cats and dwarf cats that have longer and straighter legs with healthier joints, are followed.

White, which is another dominant DNA variant in cats, is another example of a health concern associated with a phenotypic trait.[37–40] Brainstem auditory evoked response (BAER) testing is recommended to determine if white cats have partial and/or unilateral vs bilateral deafness. Some lines of white cats may produce a lower proportion of deaf cats, but why some cats are deaf and others have normal hearing is unknown. The deafness could be completely random (ie, due to the stochastic process of melanocyte migration during development) or perhaps other genetic modifiers within the genetic background of dominant *White* cats contribute to the hearing loss. Only genetic research of *White* cats that have had BAER testing will help resolve this conundrum. The effect of having two copies of the DNA variant causing dominant *White* is also unknown, but it could be theorized that two copies of the *White* DNA variant produce a higher likelihood of deafness.

The variant for *White* is large and complex and many commercial services can therefore not distinguish the *White* allele from the *Spotting* allele, which is at the same genetic (chromosomal) position and within the same gene called *KIT*.[22] Although commercial services do indicate the problem in distinguishing between the *White* and *Spotting* DNA variants, often clients do not understand the meaning of the result. Care should be taken when interpreting the reports regarding *White* and *Spotting* in cats to be sure the alleles for *White* are distinguished from the alleles of *Spotting*, which are not associated with deafness. A third variant in the *KIT* gene causes white feet (gloves) in the Birman breed,[41] but this variant does not interfere with the *Spotting* and *White* variants and is also not associated with deafness. A few laboratories, such as the University of California, Davis Veterinary Genetics Laboratory (vgl.ucdavis.edu), can distinguish between the alleles for *White* and *Spotting*.

Choosing a testing laboratory

A variety of small and large companies provide genetic testing for domestic cats. Some are purely commercial and for profit while others are research-oriented. Which testing service to select can be a conundrum for veterinarians and owners. Cheaper and more tests is not always the best selection.

Primary investigator involved in the discovery of a variant

The best resource for a genetic test is the primary investigator who was involved with the discovery of the DNA variant for the given disease or trait. The primary investigator can be identified and contacted from the information on the associated publications, which can be found on the OMIA website. Many investigators themselves offer specific genetic testing services, usually for their own discoveries. Scientific discovery will more likely progress when using the primary investigator and the veterinarian and owner will also benefit from the interactions.

First, the direct interactions between the investigator who understands the conditions in detail with the veterinarians and owners ensures appropriate genetic counseling regarding disease. Genetic counseling includes what the test result means, the consequences for the cat's health, how to proceed with healthcare, and then, also, how to conduct a mating to prevent the birth of afflicted kittens and the best ways to reduce the allele frequency in the population (see 'Dos and don'ts for genetic testing counseling advice' box). How does a breeder properly manage a carrier for a disease or undesired phenotypic trait? The answers are usually suggested by the investigators (ie, ad hoc genetic counselors).

The best resource for a genetic test is the primary investigator who was involved with the discovery of the DNA variant for the given trait or disease.

Dos and don'ts for genetic testing counseling advice

- **Do not suggest elimination of cats from breeding programs until a variant has been validated for that breed.** As discussed in the 'Large panel genetic testing' box later, a genetic test is valid only for the breed(s) in which the variant was discovered and for which published information is available. Genetic tests should be validated within a new or unrelated breed because the genetic background is different between breeds and this can cause a genetic mutation to act differently. As discussed earlier, the DNA variant may cause a later age of onset for the disease, a different or a more mild or more severe presentation, or no presentation of disease at all. Documentation of a DNA variant within a breed is not validation. Validation implies the DNA variant is proven to cause a health problem or the trait of interest.
- **Do make breeding and health decisions for DNA variants that have obviously come from related breeds.** Some tests are obviously appropriate for different and new breeds when the crosses are known or accepted by the registries, such as when a new breed is developing from a mixture of established breeds.
- **Do recommend that new cats entering a breeding program are genetically tested to be certain an unwanted DNA variant is not introduced.** Once foundation or breeding cats have been genetically tested and found to not have the DNA variant(s) of concern, no further testing is required as the offspring will not inherit the variant.
- **Do be aware of breeding practices in different cat registries.** Breeders know more about how the breeds are related and outcrossed with different breeds than veterinarians. All longhaired or shorthaired and color varieties of breeds should be considered to have the same variants and do need to be genetically tested.
- **Do be aware of outcrosses with 'similar' breeds.** Ragdolls, Siberians and Maine Coon lines have been identified with common variants that were not originally identified within the breed but in the similar breed, likely due to outcrossing. Since the genetic background has changed, disease caused by the variant needs to be confirmed.
- **Do, where possible, use serology to support genetic testing for blood typing when making breeding decisions but do not use genetic testing solely for blood type determination for healthcare procedures.** Blood type variants should be monitored in all cats (random-bred and pedigreed). The gene *CMAH*, which causes the major cat blood type, has many (14) variants listed, although only a few define the type B and type AB blood types and investigators are working to define the best set of variants to test. Currently, as many variants as possible should be tested to clarify which DNA variants in *CMAH* are the most important. Eliminating one variant over another based on one serologic or genetic test outcome is not a conservative approach. DNA testing laboratories that perform the most *CMAH* variants, as well as, ideally, serology, should therefore be used. The University of California, Davis Veterinary Genetics Laboratory (www.vgl.ucdavis.edu) has robust *CMAH* testing. Serology and cross-matching for blood type determination is the standard of care and when determining which cats to mate, serology-based tests should therefore, when possible, support the results of genetic testing. The results of blood type genetic tests can be considered but not used solely for procedures.
- **Do consider genetic tests for rare disease variants in cats with a similar presenting complaint.** These variants can be screened by an investigator studying the disease or by large panel testing services.
- **Do support the eradication of genetic diseases from cat breeding programs.** Most cat genetic diseases are rare and the populations are large enough to support reduction and/or eventual elimination. However, eradication must be accomplished slowly and with consideration of the entire cat including its health and behavior as well as its genetics.
- **Do consider precision/genomic medicine.** WGS and WES are now affordable and can identify causal variants in one case very rapidly. The identified variant could lead to a targeted therapy or help develop a new animal model for a disease.

Second, genetic testing by the investigator allows for more scientific research regarding the disease and the gene, with the patient potentially becoming part of a new genetic discovery. The investigator will likely also know more about the genetic variations and polymorphisms in the gene that are close by the actual causal DNA variant. Thus, if a genetic test provides what seems to be an inaccurate result, the investigator most likely has the samples and background knowledge to improve the genetic test in both sensitivity and specificity. Genetic testing in diverse cat populations and hybrid cat breeds can be particularly tricky as unknown DNA variation from the wild felid's DNA may affect the assay designs and the overall accuracies of the genetic tests.

Third, genetic testing provides an income for the laboratory, allowing the investigation of more aspects of the same disease or for research on other diseases and traits, leading to more genetic tests for cats. In addition, having a veterinary school behind the discoveries leads to ready access to knowledge and support for veterinary care by veterinary specialists. Current DNA tests do not predict severity and progression of the diseases; thus, veterinary healthcare surveillance is vitally important when a cat has a positive test for a genetic disease. Additionally, if a patient has a condition that already has a genetic test available and then that genetic test result is negative, the investigator may be likely to consider further studies, such as WGS or WES, to discover a new variant that may be causing the cat's condition.

The primary investigator for a variant will likely provide appropriate genetic counseling regarding the associated disease.

Large panel genetic testing

Large DNA array-based panels, which are considered a massively parallel sequencing technique, can test for hundreds to hundreds of thousands of DNA variants using DNA from buccal swabs, and these, as well as newer technology called genotyping-by-sequencing (GBS), can provide a lot of data for a low cost. There remain questions around the accuracy of these large panel tests, however, and their use has ethical, social and legal implications, many of which are common to genetic testing in both animals and humans (eg, relationship misattribution, identification of variants of uncertain significance and genetic discrimination).[42]

Accuracy

DNA arrays are highly accurate for most DNA variants; however, the operative words are 'highly' and 'most'. No array data are 100% accurate, but the question remains as to what the error rates for each test on the array and the array overall are. Since most DNA array designs are proprietary, side-by-side comparisons are lacking to determine sensitivity and specificity of genetic tests across platforms and companies.

In human medicine, because of the concern for large panel testing accuracy, the standard of practice is to request retesting using a single assay test; that is, getting a second opinion before making important health and breeding decisions. Thus, while arrays are excellent for phenotypic traits, breed origins and genetic diversity testing, as mentioned earlier, the results should be double-checked (second opinion; ideally by performing the test with a different laboratory using a different testing method) for diseases that are leading to decisions on health and breeding practices. Overall, the accuracies of disease variant results are not available using large panel testing, neither for false-positive nor false-negative results.

The use of large array-based panels has ethical, social and legal implications, many of which are common to genetic testing in both animals and humans.

Incidental secondary findings

A significant concern raised by the use of large panel testing is the discovery of a DNA variant that is not expected in a population; this is categorized as an incidental (secondary) finding. Although a breeder may use a large panel test for a specific condition, such as determining *PKD1* status, an incidental (secondary) finding of a DNA variant in a different and unexpected gene becomes a dilemma.[43] The American College of Medical Genetics (ACMG) 2019 policy statement recommends laboratories report only incidental (secondary) findings of a limited number of well-documented pathogenic alterations.[44] The list of DNA variants acceptable to report as incidental findings is updated as scientific data support the DNA variant as causal for disease in different populations and ethnic groups.[45,46] The aim of this recommendation from the ACMG policy statement is to reduce unproven healthcare interventions based solely on genotype information; in the author's opinion, the same standards need to be implemented in companion animal genetic testing.

Testing for disease-causing variants not validated in a breed

For the genetic testing of animals, a similar concern is when a DNA variant shown to cause disease in a specific breed is then tested in unrelated breeds where the association with disease has not been scrutinized by research. Direct-to-consumer commercial services, such as the 23andMe model in humans, use large genetic testing panels (via DNA array, GBS, mass spectroscopy, etc) to test for a wealth of variants that are not validated in other breeds. A DNA variant needs to be proven to cause disease within every breed that has a different genetic background to the breed in which the DNA was discovered. For instance, Abyssinians and related breeds, such as Somali, have the same genetic background and, thus, the same risk for blindness due to the *CEP290* DNA variant;[12] however, for unrelated breeds, such as Maine Coon cats, the *CEP290* mutation would need to be proven to cause blindness within the breed since the genetic background is different.[13]

The reporting of DNA variants in unrelated breeds also has advantages, such as: (1) detection of outcrossing to other breeds, whether intentionally or unintentionally; (2) if identified early, being able to quickly eliminate cats from breeding programs before the condition is spread within or to another breed (eg, see the discussion of pyruvate kinase deficiency and *CEP290* in the 'Routine genetic testing for diseases in cat breeds' section); and (3) the potential for identification of de novo variants at the same gene position. An example of this rare last scenario is human disproportionate dwarfism (achondroplasia), which is mainly caused by a specific DNA variant in *FGFR3*.[47] About 80% of achondroplastic dwarves are caused by the exact same mutation that occurs by de novo mutation; that is, the mutation occurs independently in a person more often than being spread by inheritance. Although rare, this type of recurrent de novo mutation could occur in any species, although it is not yet clearly documented in cats.

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Commercial services providing large panel tests

Commercial services want to provide a 'one-stop-shop' that fulfils the perceived need to test for dozens of traits and diseases as well as an individual's ancestry, breed and diversity. Although testing dozens to hundreds of DNA variants is required, technological improvements have supported the development of large panel testing (see 'Large panel genetic testing' box) to do just this, mostly on one technological platform, conducting one assay. As companies have competitive pressures to offer the most tests for the least amount of money, large panel testing can produce many DNA results for a low cost.

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Overall, large panel DNA testing has benefits but there are also factors to be wary of.[48–51]

Benefits include:

- If starting a new breed from random-bred cats, genetic testing for every known variant is prudent and demonstrates good breeding practices; that is, how to start a new breed on the right paw!
- Like for 23andMe for humans, it can be interesting and useful for owners or breeders to know their cat's ancestry and genetic status of phenotypes and diseases.
- Knowing breed composition may give suggestions for monitoring for diseases common to the breed ancestry.
- Large panels provide a 'one-stop-shop' for genetic test services; thus, good commercial laboratories with good customer services facilitate genetic testing, providing genetic knowledge to the consumer and the veterinarian.
- The outcrossing of variants to other breeds may be discovered and, if found early, quick elimination of the variant may be possible.
- De novo variants at the same gene position may be identified.

Factors to be wary of include:

- Although highly accurate for most variants, the accuracy of large panel testing remains undetermined.
- A DNA variant that is not expected in a population may be discovered, and unproven healthcare interventions could be carried out based solely on this information.
- Variants that are not validated in a breed may be tested for, despite the need for a DNA variant to be proven to cause disease in every breed with a different genetic background to the breed in which the DNA was discovered.
- A cat's result indicating it is a carrier for a disease variant may cause anxiety for its owner.
- Large panel testing gives the impression that a lot of important health data are obtained for the money, which is generally not true. As discussed, most cats will not have the variants for most of the diseases found in cats. Only pedigreed cats (or a small, local population) will have a higher prevalence for diseases, specifically the diseases associated within a particular breed. In addition, most genetic diseases are not 'actionable', meaning a curative therapy is not available and the management of clinical signs is the default treatment, providing no additional options for the veterinarian for healthcare.

If starting a new breed from random-bred cats, genetic testing for every known variant is prudent and demonstrates good breeding practices; that is, how to start a new breed on the right paw!

The number of genetic tests offered is not a reflection of the quality of a service, however; more tests does not imply better service. For example, some commercial services have less effective customer services, poor explanations regarding test reports and especially poor genetic counseling services. Poor counseling can lead to poor breeding decisions and unnecessary culling of animals due to misinterpretation of the test results. Further, some companies may sell their information to health industry partners and so when choosing a commercial service, the downstream use of genetic data should also be considered. While commercial services might aim to provide all the answers with large panel tests, in some instances (ie, where results might lead to decisions on health and breeding practices), a second opinion should be sought due to the undetermined accuracy of these tests.

Beware of one trick ponies

Companies that have different DNA technologies available to complete the genetic testing should be used where possible. DNA variants can be simple or complex DNA changes and a DNA array has limitations for some DNA changes due to how the technology works. DNA variants due to large rearrangements or insertion/deletions of sequence are challenging to genotype on DNA arrays as well as with the newer GBS technologies (see the discussion of *White/Spotting* testing in the 'Aesthetic phenotypic traits associated with health concerns' section). Some commercial services perform the vast majority of their testing using a DNA array and then have a subsidiary laboratory conduct the tests that fail array design. Companies may not make clear what technologies they have use of, however, and so will most likely need to be asked.

When choosing a commercial service providing a large panel genetic test, more tests are not necessarily better and the quality of the service is important to consider.

KEY POINTS

- Genetic testing is another diagnostic tool for the veterinary healthcare toolkit.
- One of the most important reasons for genetic testing is to identify carriers for recessive conditions. For dominant traits, genetic testing is used to determine how many copies of a trait are present and which variant is present if several are possible. Further, genetic tests help to indicate which cats may need life-long monitoring and health management.
- A second opinion is warranted when making breeding decisions, including neutering and removing a cat from a breeding program, based on DNA variant results from a large panel test.
- Most genetic diseases could be eradicated from cat breeds with minimal effort if consistent and widespread genetic testing is implemented by all cat registries for a few years. Some genetic diseases will need slower eradication than others to prevent potential inbreeding depression, and care needs to be taken in the rapid removal of cats with common diseases, such as HCM, from breeding programs.
- In the case of large panel genetic testing, more tests are not necessarily better, and it is best to work with laboratories invested in a particular disease and commercial services that provide good customer care with genetic counseling to the owner and the veterinarian.
- New DNA variants for heritable disease can be identified faster than ever before. Precision/genomic medicine is therefore becoming increasingly worth considering in veterinary healthcare.

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ORCID iD

Leslie A Lyons https://orcid.org/0000-0002-1628-7726

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