Utilizing Genetic Tests and Health Screenings in Planned Breedings

Eddie Dziuk  
OFA Chief Operating Officer  
Havanese National  
August 8, 2018
Introduction

- Eddie Dziuk
  - OFA Chief Operating Officer, 2001 - ...
  - ‘85 BS Economics – Mt St Mary’s
  - ‘09 MBA – UMKC
  - Currently enrolled in U of MO Masters program for Data Science and Analytics
  - Involved in Purebred dogs since ’76
  - Breeder/Exhibitor/Judge
  - AKC Delegate
  - Disclosure: NOT a DVM
Utilizing Genetic Tests & Health Screening in Planned Breedings

• Daunting task to cover thoroughly in an hour
  – Variety of Topics
    • Ethics & Responsibilities
    • Genetics
      – Population Genetics
  • Application
    – Variety of Knowledge and Experience Base
Ethical/Responsible Dog Breeding

• Who is a dog breeder?
  – Someone that produces a litter of puppies
    • Purebred or Mixed
    • Purposeful/Planned or Accidental
Ethical/Responsible Dog Breeding

• Who Breeds? What Motivates Them? How Educated Are They?
  – Accidental
  – Casual (“Backyard”)
    • No Health Testing
    • Selection often based on convenience
    • Few, if any, criteria for puppy placement
    • Motivation varies but might be financial or emotional
  – Commercial / High Volume
    • Business – has implications on health testing, selection, puppy placement, etc.
  – Purposeful Hobby Breeders
    • Ideally motivated by passion for the breed, thoughtful selection, and a desire to achieve quality
    • Does not inherently equate to “Responsible Breeders”
Ethical/Responsible Dog Breeding

- Who Breeds? What Motivates Them? How Educated Are They?
  - Accidental
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- As a dog breeder, whether you realize it or not – to some degree you are also geneticists – "Every time you conduct a breeding, you are conducting a genetics experiment"  Dr. Danika Bannasch, NPCCHC 2013
Ethical/Responsible Dog Breeding

• No breeder intentionally wants to produce puppies that will suffer from genetic disease
• But, it’s the actions taken up front to limit genetic disease that helps differentiate “Responsible Breeders” from the others

• “Responsible Breeder” Breeding Goals
  – Maintain and enhance the quality of the breed
    • In accordance with the Standard
    • Soundness, Temperament, Type, Function
  – Manage/Limit Genetic Disease
Ethical/Responsible Dog Breeding

Assuming we all agree that HEALTH is a major component of responsible dog breeding…

What is the only way to positively select for genetically healthy offspring?

Through the selection of genetically healthy parents!
Managing Genetic Disease – Genetic Testing

- Phenotypic Tests – Tests to identify clinically affected and normal individuals
- Genotypic Tests – Direct DNA tests for liability genes
- Pedigree Analysis – make assumptions regarding underlying genetic status, and identify carrier risk based on knowledge of disease status within the pedigree
- Estimated Breeding Values (EBVs)

- All genetic disease cannot be prevented. However, we have the knowledge and the tools to improve the genetic health of our puppies!
Phenotypic Tests

- Phenotypic Tests – Tests to identify clinically affected and normal individuals
  - Hip Dysplasia
  - Elbow Dysplasia
  - Congenital & Adult Onset Cardiac Disease
  - Congenital Deafness
  - Ocular Disease
  - Autoimmune Thyroiditis
  - Patellar Luxation
Phenotypic Tests & Pedigree Analysis

- Depth AND Breadth
- Selecting FOR Healthy Genes
- Selecting AGAINST Deleterious Genes

<table>
<thead>
<tr>
<th></th>
<th>Paternal Gr-Sire “Fair”</th>
<th>Paternal Gr-Sire “Fair”</th>
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<tbody>
<tr>
<td>Sire “Good”</td>
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<tr>
<td>Paternal Gr-Dam “Good”</td>
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<td>Paternal Gr-Dam “Good”</td>
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<td>Stud Dog A “Fair”</td>
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<td>Dam “Good”</td>
<td>Maternal Gr-Sire “Good”</td>
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<td>Maternal Gr-Dam “Good”</td>
<td>Maternal Gr-Dam “Good”</td>
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## Phenotypic Tests & Pedigree Analysis

- Depth AND Breadth
- Selecting FOR Healthy Genes
- Selecting AGAINST Deleterious Genes

<table>
<thead>
<tr>
<th>1st Generation</th>
<th>2nd Generation (Parents, Aunts, Uncles)</th>
<th>3rd Generation (Gr-parents, Gr-Aunts, Gr-Uncles)</th>
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<tr>
<td>Sibs (6):</td>
<td>Sibs (8):</td>
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<td>Sibs (7):</td>
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<tr>
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<tr>
<td>Fair</td>
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<tr>
<td><strong>Sib “Good”</strong></td>
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<td>Sibs (9):</td>
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<tr>
<td>Good</td>
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<tr>
<td>Dam “Good”</td>
<td><em>Paternal Granddam “Good”</em></td>
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<tr>
<td>Sibs (10):</td>
<td>Sibs (8):</td>
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<td>Good</td>
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<tr>
<td>Good</td>
<td>Good</td>
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<tr>
<td><strong>Sib “Excellent”</strong></td>
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<td>Excellent</td>
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<td>Maternal Grandsire “Good”</td>
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<tr>
<td>Sibs (?)</td>
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<td>Maternal Granddam “Good”</td>
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<td>Sibs (9):</td>
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<tr>
<td>Good</td>
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</table>
Phenotypic Tests & Pedigree Analysis

- Depth AND Breadth
- Selecting FOR Healthy Genes
- Selecting AGAINST Deleterious Genes

Stud Dog B “Good”
- Sibs (9):
  - Fair
  - Fair
  - Good
  - {dysplastic}

Sire “Good”
- Sibs (7):
  - Fair
  - Good
  - Good
  - {dysplastic}

Paternal Grandsire “Fair”
- Sibs (7):
  - Fair
  - Good
  - Good

Paternal Granddam “Good”
- Sibs (?)

Dam “Good”
- Sibs (6):
  - Fair
  - Fair
  - {dysplastic}

Maternal Grandsire “Good”
- Sibs (10)
  - Fair
  - {dysplastic}
  - {dysplastic}
  - {dysplastic}

Maternal Granddam “Good”
- Sibs (6):
  - Fair
  - Good
  - Excellent
Phenotypic Tests & Pedigree Analysis

- Polygenic Disease: Threshold Traits
Phenotypic Tests – example Hips

- Progeny results of matings between parents with known hip scores (N=490,966)
  - Excellent = 1
  - Good = 2
  - Fair = 3
  - Borderline = 4
  - Mild = 5
  - Moderate = 6
  - Severe = 7
  - Examples
    - Excellent Sire x Excellent Dam: 1+1 = 2
    - Excellent Sire x Fair Dam: 1+3 = 4
    - Fair Sire x Fair Dam: 3+3 = 6
    - Mild Sire x Fair Dam: 5+3 = 8

Phenotypic Tests – example Hips

• Progeny results of matings between parents with known hip scores (N=490,966)

Phenotypic Tests – example Elbows

- Progeny results of matings between parents with known elbow scores (N=67,599)

Fig. 2. Relationship of Combined Parent Score to percentage of elbow dysplastic progeny.

Managing Polygenic Disease

• Examples: cardiac anomalies, hip & elbow dysplasia, patellar luxation
• Identify phenotypic traits tied to the underlying genes
• Phenotypic breadth of pedigree provides information on the possible range of genes carried
• Treat disorders as threshold traits
• Breed normal dogs from (mostly) normal litters to select for normalcy
Genotypic Tests

• Genotypic Tests – DNA tests for liability genes
  – Direct Mutant Gene Tests
    • vWD (von Willebrands), PRA (Progressive Retinal Atrophy)
    • Havanese:
      – Factor VIII Deficiency (VetGen)
      – Neonatal Ataxia (U of Missouri)
  – Known mutations in the bases (CGAT) in the nucleotides that make up DNA
    • Can be Insertions, Deletions, Base Pair Changes
Genotypic Tests

- Genotypic Tests – DNA tests for liability genes
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Missense mutation

Original DNA code for an amino acid sequence.

<table>
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<tr>
<th>DNA bases</th>
<th>C</th>
<th>A</th>
<th>T</th>
<th>C</th>
<th>A</th>
<th>T</th>
<th>C</th>
<th>A</th>
<th>T</th>
<th>C</th>
<th>A</th>
<th>T</th>
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<tbody>
<tr>
<td>Amino acid</td>
<td>His</td>
<td>His</td>
<td>His</td>
<td>His</td>
<td>His</td>
<td>Pro</td>
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</tbody>
</table>

Insertion mutation

Original DNA code for an amino acid sequence.

| DNA bases | C | A | T | C | A | T | C | A | T | C | A | T | C | C | T | C | A | T | C |
| Amino acid | His | His | His | His | His | Pro | His |

Deletion mutation

Original DNA code for an amino acid sequence.

| DNA bases | C | A | T | C | A | T | C | A | T | C | A | T | C | A | T | C | A | T | C |
| Amino acid | His | His | His | His | His | Pro | His |

Incorrect amino acid sequence, which may produce a malfunctioning protein.
Genotypic Tests

• 2001: handful commercially available DNA tests...vWD, PRA, SNB, CY
# Genotypic Tests

**2018 (146 OFA registerable DNA Tests)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Genotype</th>
<th>Genotype Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Onset Neuropathy</td>
<td>DVDDB (DNGS)</td>
<td>Lafora Epilepsy</td>
</tr>
<tr>
<td>Adult Paroxysmal Dyskinesia</td>
<td>Early Retinal Degeneration</td>
<td>Lagotto Storage Disease</td>
</tr>
<tr>
<td>Agoudi</td>
<td>Eccotermal Dysplasia</td>
<td>Lebergen Polyneurupathy (LPN1)</td>
</tr>
<tr>
<td>Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)</td>
<td>Episodic Falling</td>
<td>Lebergen Polyneurupathy 2 (LPN2)</td>
</tr>
<tr>
<td>Benign Familial Juvenile Epilepsy</td>
<td>Exercise Induced Collapse</td>
<td>Leukoencephalomyelopathy (LEMF)</td>
</tr>
<tr>
<td>Buff</td>
<td>Factor VII Deficiency</td>
<td>Lupoid Dermatosis</td>
</tr>
<tr>
<td>Canine Leukocyte Adhesion Deficiency (CLAD)</td>
<td>Factor VIII Deficiency</td>
<td>Macrothrombocytopenia</td>
</tr>
<tr>
<td>Canine Multifocal Retinopathy</td>
<td>Factor XI Deficiency</td>
<td>Multiple Drug Resistance (MDR1)</td>
</tr>
<tr>
<td>Canine Multiple System Degeneration (CMSD)</td>
<td>Familial Enamel Hypoplasia (FEH)</td>
<td>Muscular Dystrophy</td>
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<tr>
<td>Centronuclear Myopathy</td>
<td>Familial Nephropathy</td>
<td>Myocobacterium Avian Complex</td>
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<tr>
<td>Congenital Axonopathy</td>
<td>Factor VIII Deficiency</td>
<td>Myotonia Congenital</td>
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<tr>
<td>Cerebellar Axatia</td>
<td>Fucosidosis</td>
<td>Myoglobinuria</td>
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<td>Cerebellar Degeneration</td>
<td>Gangliosidosis (GM1)</td>
<td>Myopathology</td>
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<tr>
<td>Cleft Lip/Palate and Syndactyly</td>
<td>Gangliosidosis (GM2)</td>
<td>Musculin-Liuee Syndrome</td>
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<tr>
<td>Cleft Palate (CP1)</td>
<td>Glanzmann’s Thrombasthenia</td>
<td>Progressive Retinal Atrophy (PRD3)</td>
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<tr>
<td>Cobalamin Malabsorption</td>
<td>Globoid Cell Leukodystrophy</td>
<td>Progressive Retinal Atrophy (Type A)</td>
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<tr>
<td>Collie Eye Anomaly</td>
<td>Glycogen Storage Disease Type IIIa (GSD IIIa)</td>
<td>Narcolepsy</td>
</tr>
<tr>
<td>Cone Degeneration</td>
<td>Hemophilia A</td>
<td>Neurofibromatosis (NME)</td>
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<tr>
<td>Cone Rod Degeneration (crid3)</td>
<td>Hemophilia B</td>
<td>Progressive Retinal Atrophy (PRD1)</td>
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<tr>
<td>Cone Rod Dystrophy 2 (crid2)</td>
<td>Hereditary Cataract (HSF4-1)</td>
<td>Progressive Retinal Atrophy (PRD2)</td>
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<tr>
<td>Congenital hypothyroidism with Goiter</td>
<td>Hereditary Cataract (HSF4-2)</td>
<td>Progressive Retinal Atrophy (PRD3)</td>
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<tr>
<td>Congenital Macrothrombocytopenia</td>
<td>Hereditary Footpad Parakeratosis (HFPK)</td>
<td>Progressive Retinal Atrophy (PRD3)</td>
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<tr>
<td>Copper Toxicosis</td>
<td>Hereditary Axonal Dystrophy (NAD)</td>
<td>Progressive Retinal Atrophy (PRD3)</td>
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<td>Craniofacial Osteopathia</td>
<td>Hereditary Nucleating Myopathy (ENMM)</td>
<td>Progressive Retinal Atrophy (PRD3)</td>
</tr>
<tr>
<td>Cystic Neurorhopia (Gray Collie Syndrome)</td>
<td>Hereditary Nephritis</td>
<td>Progressive Retinal Atrophy (PRD3)</td>
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<td>Cystinuria Type 1A</td>
<td>Histioytic Sarcoma</td>
<td>Progressive Retinal Atrophy (PRD4)</td>
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<tr>
<td>Cystinuria Type 2A</td>
<td>Hyperuricosuria</td>
<td>Progressive Retinal Atrophy (PRD4)</td>
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<td>Cystinuria Type 3</td>
<td>Hypomelanin</td>
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<td>D Locus - dilute pigment</td>
<td>Ichthyosis</td>
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<tr>
<td>Degenerative Encephalopath</td>
<td>Inherited Metabolism</td>
<td>Progressive Retinal Atrophy (PRD4)</td>
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<td>Degenerative Myelopathy</td>
<td>Inherited Myelopathy</td>
<td>Progressive Retinal Atrophy (PRD4)</td>
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<td>Degenerative Myelopathy SOD1B</td>
<td>Juvenile Addison’s Disease (JADD)</td>
<td>Progressive Retinal Atrophy (PRD4)</td>
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<td>Dermatomyositis</td>
<td>Juvenile Dilated Cardiomyopathy (JDC)</td>
<td>Progressive Retinal Atrophy (PRD4)</td>
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<td>Dilated Cardiomyopathy (DCM)</td>
<td>Juvenile Laryngeal Paralysis &amp; Polyneurupathy (JLPP)</td>
<td>Progressive Retinal Atrophy (PRD4)</td>
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<tr>
<td>Dilated Cardiomyopathy (DCM1 &amp; DCM2)</td>
<td>Juvenile Myotonic Epilepsy</td>
<td>Progressive Retinal Atrophy (PRD4)</td>
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<tr>
<td>Dominant Black</td>
<td>L2HGA</td>
<td>Progressive Retinal Atrophy (PRD4)</td>
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<tr>
<td>Dry Eye Curly Coat Syndrome</td>
<td>LAD3</td>
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*Note: This list is not exhaustive and represents a selection of genotypic tests available for dogs.*
Genotypic Tests

- 39 Chromosomes
- Mode of Inheritance: Single Autosomal Recessive

<table>
<thead>
<tr>
<th>Parent 1 Status</th>
<th>Normal/Clear</th>
<th>Carrier</th>
<th>Affected</th>
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<tr>
<td>Normal/Clear</td>
<td>All = Normal/Clear</td>
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<td>All = Carrier</td>
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<td>Carrier</td>
<td>1/2 = Normal/Clear</td>
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<tr>
<td>Affected</td>
<td>All = Carrier</td>
<td>1/2 = Carrier</td>
<td>1/2 = Affected</td>
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</table>
Genotypic Tests

- Genotypic Tests – DNA tests for liability genes
  - Linkage or Haplotype Tests
  - Test chromosomal region rather than the exact (unknown) mutation – as a result some margin of error possible
Genotypic Tests

- **Other complicating variables**
  - Incomplete Penetrance – Disease mutation present but the dog appears clinically normal
  - Modifying Genes
  - Environmental Influence
  - ???

- **Expressivity** – Dogs with the same mutation manifest the trait or disease to different degrees (example Brindle)

- **Epistasis** – One mutation masks the effects of another (example White Boxer)

- **Risk Susceptibility** – Mutation confers risk, but may not be the only cause (DM)
Genotypic Tests

• Proliferation of Labs
  – No central certifying organization
    • Processes, Procedures, Use of Known Control Samples
    • IPFD – International Partnership for Dogs has begun to address this issue

• Breed Specificity

• Multiple mutations can cause the same disease expression
  • PRA in Golden Retrievers
### Genotypic Tests

- **Proliferation of Labs**

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<thead>
<tr>
<th>Animal Genetics</th>
<th>Genetic Technologies (Australia)</th>
<th>Michigan State University</th>
<th>University of Copenhagen</th>
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<tr>
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<td>Genomia</td>
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<td>University of Minnesota/Canine Genetics Lab</td>
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<td>GenSol</td>
<td>Optigen</td>
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<td>UC Davis - VGL</td>
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<td></td>
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<td>Wisdom Health</td>
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Take Aways

• Breeders must consider many aspects in their selection criteria – conformation, temperament, working ability, health
• An individual is not an eye, a hip, or a heart. Each individual carries tens of thousands of genes, and each is a part of the breed’s gene pool
• Breeding decisions based on a single testable gene or phenotypic test are often inappropriate, must factor:
  – appropriateness of the test
  – severity of the disease – quality of life
  – prevalence in the breed population
  – size of the overall gene pool
• Use Health Screening as a TOOL to apply selective pressure to produce healthier dogs!
Havanese CHIC Requirements

- Hip Dysplasia
  - Either OFA or PennHIP
- Eye Examination
- Patellar Luxation
- Congenital Deafness

- As of 8/7/18: 2,889 CHIC Havanese