SHORT COMMUNICATION

PETscan: measuring incidence of disease phenotypes to prioritize genetic studies in companion animals

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Summary

Reliable incidence measurement of diseases is necessary for identification of hereditary diseases in companion animal populations. The data collection system 'PETscan' was developed to facilitate standardized registration of diagnoses in veterinary practice. In the development, we attempted to counter challenges known from other primary practice data systems. PETscan includes a comprehensive list of potential diagnoses and supports the veterinary professionals in the diagnostic process. Demographics, individual data and standardized diagnostic data are collected through practice management software in a central database for epidemiological analysis. A preliminary data analysis from PETscan showed specific health issues in four canine breeds. As a real-time prospective monitoring tool, PETscan summaries can objectively assess the incidence of disorders in companion animal populations and can be used to prioritize disease–gene identification studies and evaluate the effects of breeding strategies, for example, after implementation of a new DNA test in the breeding strategy.

Keywords diagnosis, genetic disorder, population-based prospective monitoring tool

Inbreeding and selection for specific phenotypic characteristics have resulted in health and welfare issues in companion animal populations, initiating public debate. Inbreeding and selection for desired, but unhealthy, breed standards often lead to a higher frequency of recessive defects within a population. At the same time, increased disease frequency in a genetically homogeneous population creates an opportunity for discovery of causal genes (Van Steenbeek *et al.* 2016). This also creates the opportunity of a dog model for human diseases, as shown by the collaborative LUPA initiative (Lequarré *et al.* 2011).

The first step in prioritizing genetic studies is having knowledge about disease incidence in specific populations; however this is largely undocumented (Collins *et al.* 2011). We developed the data collection system 'PETscan' to document disease phenotypes in companion animal populations via veterinary practice management software (PMS).

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PETscan enables prospective collection of standardized diagnostic data. The PMS of a veterinary practice is connected to a central MySQL database, allowing information to be shared and used for epidemiological analyses (R Core Team 2016). PETscan opens from the PMS and is organised as a branching tree, which is set up according to organ system, anatomic location and diagnosis to mimic the medical reasoning in veterinary practice. Multiple diagnoses per individual and consultation may be entered. 'No abnormalities' can be selected at a preventive consultation of a healthy animal or a repeat consultation.

PETscan information includes: demographic data (species, breed, sex, date of birth), unique identification (transponder code) and consultation information (practice code, date, weight, neuter status and diagnosis). PETscan was evaluated in a pilot study, for which participating practices were equally distributed throughout the Netherlands. Dog breeds evaluated in the pilot phase of PETscan included Chihuahua, French Bulldog and Labrador Retriever with mixed breed as a heterogeneous control group.

To illustrate the potential of PETscan data, we compared preliminary results of occurring organ system entries and specific diagnoses in these groups to other companion animal population studies (LaFond *et al.* 2002; Asher *et al.*

2009; Summers *et al.* 2010; O'Neill *et al.* 2014b; Mattin *et al.* 2015; Mochizuki *et al.* 2017). Between September 1, 2015 and September 1, 2017, 6162 diagnoses were entered into PETscan. The overall data included 3224 individual dogs, of which 47.6% were female dogs. Labrador Retriever (*n* = 276), Jack Russell Terrier (*n* = 203), French Bulldog (*n* = 94) and Chihuahua (*n* = 90) were the four most common breeds. Mixed-breed dogs comprised the largest group of dogs (*n* = 579). In the four populations, the percentage of females ranged from 44 to 50%, and 50 to 65% of the dogs were born after the year 2010.

Individuals with at least one entry in PETscan per unique organ system are represented in Fig. 1a. As a comparison, the number of hereditary diseases, with or without a known mutation, reported as Mendelian traits in the Online Mendelian Inheritance in Animals database (OMIA, www. omia.org, 20180222) are also shown by organ system (Fig. 1b).

Within organ system, diagnoses that were entered most frequently in PETscan for the Chihuahua, French Bulldog, Labrador Retriever and mixed-breed dogs were compared to diagnoses reported in other pet population studies. Studies that showed similar findings are indicated in Table 1. The percentage coded as 'no abnormalities' was approximately three times lower in the French Bulldog (11%) compared to the other dog populations (28–35%) (Table 1). Surprisingly, only 1% of the diagnoses in the French Bulldog were coded as brachycephalic obstructive syndrome (BOS), which seems low because the national breed population is considered genetically predisposed to upper respiratory tract disorders such as BOS, amongst others (Keijser *et al.* 2017). In a study on conformational risk factors, 89% of the 214 French Bulldogs were affected by BOS (Liu *et al.* 2017). The current study population consisted mainly of adult individuals, so issues with BOS should have been apparent (O'Neill *et al.* 2018). Possibly, Dutch veterinarians accept BOS as the 'normal' phenotype in French Bulldogs and therefore did not register it as a diagnosis in PETscan (Packer *et al.* 2012).

O'Neill *et al.* (2014a) reviewed specific advantages and limitations of data sources for population estimates. Limitations include: questionable representativeness and excluded disorders in insurance databases, referral bias in referral clinic data, diagnostic unreliability, technical complexities, poor representativeness in cancer registries, validation issues in questionnaire data, selection bias in health schemes and underreporting and poor generalizability in specific surveillance systems (e.g. pharmacovigilance). Specific challenges for practice data include labor intensiveness, confidentiality, unsustainability, lack of structured coding, large volumes of data and lack of completeness for all events. In PETscan, we counter the challenges of primary practice data systems: diagnoses are organized and coded according to a clinical rationale, all events are registered including health checks and end-of-life events, diagnoses are automatically sent to the central database without owner information and the standardized coding allows for automated analysis of large volumes of data, creating a sustainable system. Practices that participated in this pilot study of PETscan represented those based in cities
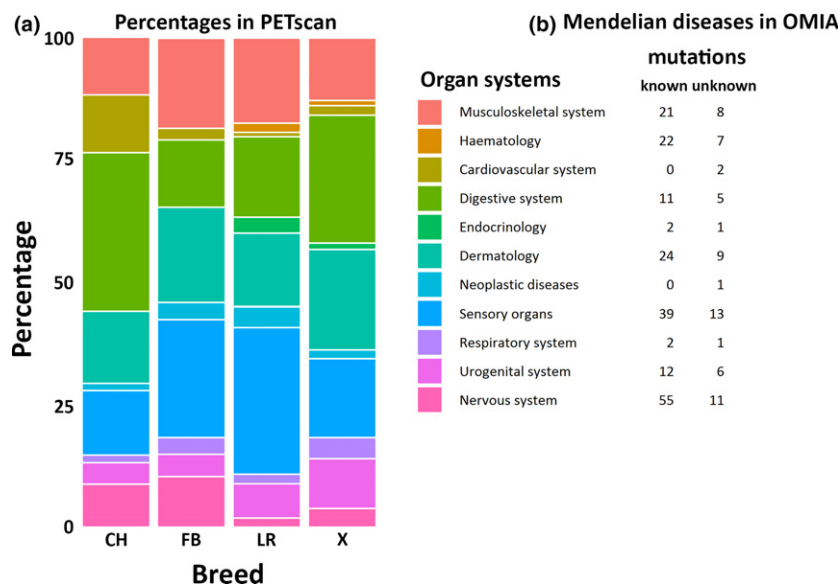

Figure 1 (a) Percentage of unique organ system entries per dog population. Individuals may have multiple organ systems entered. Breeds shown are the Chihuahua (CH, 68 entries for 66 individuals), French Bulldog (FB, 87 entries for 85 individuals) and Labrador Retriever (LR, 213 entries for 200 individuals) versus mixed-breed dogs (X, 391 entries for 368 individuals) registered in the practice-based monitoring system PETscan in The Netherlands between September 1, 2015 and September 1, 2017. (b) Number of diseases per organ system from (a) reported as Mendelian traits in the Online Mendelian Inheritance in Animals database (OMIA), with known and unknown mutation.

Table 1 Specific diagnoses most frequently entered per breed (CH, Chihuahua; FB, French Bulldog; LR, Labrador Retriever) versus mixed-breed dogs (X) registered in the practice-based monitoring system PETscan in The Netherlands between September 1, 2015 and September 1, 2017. Comparable companion animal population studies that show the same diagnoses occurring in these breeds are referenced.

Breed	*n* (individuals)	'No abnormalities' entries (%)	One or two most frequently entered specific diagnosis (*n*) (reference)	
CH	90	28	Post-formative dental issues (8) (O'Neill *et al.* 2014b)	Cardiac valve degeneration (8) (Asher *et al.* 2009; Summers *et al.* 2010; Mattin *et al.* 2015)
FB	94	11	Skin neoplasia (6) (Mochizuki *et al.* 2017)	–
LR	276	30	Otitis externa (53) (O'Neill *et al.* 2014b)	Arthrosis/Arthritis (14) (LaFond *et al.* 2002; Asher *et al.* 2009)
X	579	35	Otitis externa (43) (O'Neill *et al.* 2014b)	Anal gland disease (23) (O'Neill *et al.* 2014b)

and rural areas and varied according to size of the clinic and level of care; therefore we assumed an unbiased sample of the pet population. However, variation in veterinary opinion on breed-specific health issues should be included in the interpretation of the results and representativeness discussed.

The entering of a diagnosis into PETscan requires active participation of the veterinarian, which may be subject to variation caused by time and effort and is considered the biggest challenge in this population data system. However, diagnoses in the breed populations evaluated in the pilot phase of PETscan were similar, as reported in comparable population survey studies that did not require such participation, suggesting that PETscan data can provide a valid random sample of veterinary diagnoses in the companion animal population. Evaluation of participation levels is needed to assess whether the sample size reflects the actual number of visits in practice.

The feedback from the PETscan pilot phase has been used in an expanded version (2.0) with an elaborated diagnosis list, including infectious diseases that may be analysed geographically and pop-up advice for every diagnosis, which provides the veterinarian with a summary of diagnostic possibilities and additional useful information such as information about availability of DNA tests for hereditary diseases (Fig. S1). As a long-term project, PETscan will need to be evaluated continuously, expanding the diagnostic list with any missing or new diagnoses. The intended implementation in university clinics will ensure the evaluation by the veterinary specialists.

Population-based measurement of disease incidence can give insight into breed predisposition for disease, providing data for prioritization of genetic studies. A first breed-specific screening may be done by organ system (Fig. 1a,b) followed by more detailed analyses of diagnoses. The number of mutations in the OMIA database per organ system in comparison to the PETscan entries shows discrepancies that suggest that OMIA is a representation of specific study interests and findings, mostly monogenic, and not a representation of disease frequency. We compared the number of Mendelian diseases reported in OMIA for the Chihuahua, French Bulldog and Labrador Retriever: 22

diseases for various organ systems are registered for the Labrador Retriever, and for the Chihuahua and the French Bulldog, 2 and 1 respectively are registered. The overrepresentation of the Labrador in OMIA may be due to the long-term popularity of the breed on an international level, resulting in a research and publication bias. Another cause for overrepresentation may be reduced heterogeneity of the Labrador when compared to the Chihuahua and the French Bulldog, which increases the risk of Mendelian disorders. However, the median genetic diversity in the three breeds, as available from a tested subset of individuals (MyDogDNA, www.mydogdna.com), seemed comparable—Chihuahua, 39.8%; French Bulldog, 34.3%; Labrador Retriever, 35.5% —as measured by the genome-wide screening of thousands of sites in the individual DNA. A third cause could be that the Chihuahua and the French Bulldog are more prone to disorders caused by extreme conformation, which are less likely to show up in the OMIA database (Keijser *et al.* 2017).

PETscan offers quality assurance in the diagnostic process and standardized coding of diagnostic terminology, which allows for routine periodic data and trend analysis. As it moves from the pilot phase, PETscan allows for quantification of genetic disease issues in the companion animal population, thus allowing for prioritization of genetic studies as well as evaluation of breeding strategies.

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Supporting information

Additional supporting information may be found online in the Supporting information section at the end of the article.

Figure S1. PETscan main list with organ systems and conditions, elaborated with the pathway to the diagnosis of cardiac valve degeneration, including a diagnostic pop-up advice to support veterinary decision making as provided in the expanded version 2.0.