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Rare and unique adaptations to cancer in domesticated species: An untapped resource?

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Abstract

Strong and ongoing artificial selection in domestic animals has resulted in amazing phenotypic responses that benefit humans, but often at a cost to an animal's health, and problems related to inbreeding depression, including a higher incidence of cancer. Despite high rates of cancer in domesticated species, little attention has been devoted to exploring the hypothesis that persistent artificial selection may also favour the evolution of compensatory anticancer defences. Indeed, there is evidence for effective anti-cancer defences found in several domesticated species associated with different cancer types. We also suggest that artificial selection can favour the "domestication" of inherited oncogenic mutations in rare instances, retaining those associated to late and/or less aggressive cancers, and that by studying these seemingly rare anticancer adaptations, novel cancer treatments may be found.

KEYWORDS

cancer, domestication, domestication syndrome, evolution, evolutionary mismatch, selection

1 | INTRODUCTION

Humans have exerted artificial selection on plants and animals since the Mesolithic, resulting in the evolution of numerous domestic species (Driscoll, Macdonald, & Brien, 2009; Larson & Fuller, 2014). In stark contrast to natural selection that shapes an organism's traits to maximize individual fitness, artificial selection favours individuals displaying attributes that are, for myriad reasons, relevant to humans (Zeder, 2012). Depending on the biology of the considered species and the nature and intensity of the domestication process, domesticated species display particular biological modifications, including health related ones, compared to their wild ancestors (referred to as the "domestication syndrome," e.g. Wilkins, Wrangham, & Tecumseh Fitch, 2014).

The health related consequences of domestication can be beneficial or detrimental to a species relative to its ancestry. For instance, immune-related genes can evolve rapidly during the domestication processes (Glazko, Zybaylov, & Glazko, 2014; Jennings & Sang, 2019), as heightened immune performances improve the survival rate of individuals experiencing confinement or living at high density (Dong et al., 2015; Douxfils et al., 2011; Kuhlman & Martin, 2010). Conversely, human preferences for specific traits can increase pathological vulnerability, as selective breeding may lead to inbreeding depression and/or a concentration of deleterious alleles responsible for genetic diseases. In dogs, examples of such breed-specific diseases are retinal atrophy, neuropathy and ichthyosis (a genetic dermatosis) (André, Guaguère, Chaudieu, Genevois, & Devauchelle, 2017). Many domesticated animals (e.g. dogs, cats, cattle, horses) frequently develop cancer (Brodey, 1979; Madewell, 1981; Rowell, McCarthy, & Alvarez, 2011) (Table 1). Further, the incidence of several kinds of cancer in domestic animals is much higher than in humans, with dogs and cats often cited as familiar examples (see table 2 in Vail and Thamm (2004)).

However, little attention is devoted to exploring the possibility that domestication may represent a unique selective context favouring the evolution of enhanced resistance and/or tolerance to cancer, particularly in long-lived domestic taxa like pets. Similarly, for cancers with underlying congenital causes, we could predict that artificial selection should retain through time inherited oncogenic mutations leading to late and/or less aggressive cancers, thus "domesticating" these mutations.

TABLE 1 Example of cancer types occurring in domesticated animals

Common name	Species	Domesticated from	Time of domestication (years ago)	Predominant types of cancer	Reference
Dog	*Canis familiaris*	*Canis lupus* (Grey wolf)	15,000	Mammary tumours in females, lymphoma and mast cell tumours	Paoloni and Khanna (2008); Thalmann et al. (2013); Boerkamp et al. (2014); Baioni et al. (2017)
Cat	*Felis catus*	*Felis sylvestris lybica*	10,000	Lymphoma	Dorn (1967); Dorn et al. (1968); Driscoll et al. (2007); Driscoll et al. (2009); Vigne et al. (2016)
Ferret	*Mustela putorius furo*	*Mustela putorius* (European polecats)	2,500	Adrenal and pancreatic tumours, lymphoma	Avallone et al. (2016); Schoemaker (2017)
Pig	*Sus scrofa domesticus*	*Sus scrofa* (Wild boars)	9,000–10,000	Lymphoma	Bastianello (1983); Groenen (2016)
Goat	*Capra hircus*	*Capra aegagrus* (Bezoar)	10,000	Skin cancer, lymphoma	Bastianello (1983); Löhr (2013)
Horse	*Equus callabus*	*Equus ferus*	5,500	Skin cancers, lymphoma	Knowles, Tremaine, Pearson, and Mair (2016); Gaunitz et al. (2018)
Guinea pig	*Cavia porcellus*	*Cavia tschudii*	5,000	Lymphoma	Congdon and Lorenz (1954); Walker, Soto, and Spotorno (2014); Evans, Harr, Thielen, and MacNeill (2018)
Domestic laying hen	*Gallus gallus domesticus*	*Gallus gallus* (Red jungle fowl)	8,000	Ovarian cancer	Fredrickson (1987); Tixier-Boichard, Bed'hom, and Rognon (2011); Johnson and Giles (2013)
Cow	*Bos taurus taurus*	(Aurochs)	10,000–10,500	Skin cancer, bovine leukaemia	Madewell, 1981; Bollongino et al. (2012); Decker et al. (2014)
Sheep	*Ovis aries*	*Ovis vignei*, *Ovis ammon*, *Ovis orientalis*[a]	8,000–11,000	Skin cancer, jaagsiekte sheep retrovirus-associated lung cancer	Lloyd (1961); Palmarini, Fan, and Michael Sharp (1997); Wang et al. (2019)

[a]The exact ancestor of the sheep remains unknown.

Here, we discuss the evolutionary consequences of domestication in relation to cancer development and progression. We argue that strong and ongoing directional selection on particular traits in domestic animals, along with resultant high cancer incidence, may provide a selective environment that could generate evolutionary "solutions" to fighting cancer that is not evident in humans or wildlife.

2 | HOW COULD DOMESTICATION LEAD TO NOVEL ANTICANCER ADAPTATIONS?

In natural environments, the evolution of cancer suppressive mechanisms is weighted against other fitness-related functions (Jacqueline et al., 2017) in a manner akin to the high cost of immune system functioning leads to trade-offs with various life history traits and demands (van der Most, Jong, Parmentier, & Verhulst, 2011; Norris & Evans, 2000). Conversely, domesticated species usually live in environments that are unaffected by natural constraints such as competition, parasitism, predation or food limitation. This has at least two important implications in a cancer context: (a) domesticated animals, all things being equal, could theoretically invest more resources into fuelling their existing anticancer defences, and (b) if costly anticancer defences (resistance or tolerance) appear, they are more likely to be maintained in a protected environment devoid of threats as opposed to a natural ecosystem. When artificial selection exerts stronger coefficients of selection than any natural processes in the wild, it theoretically opens the window for the selection of unprecedented anticancer defences (Vittecoq et al., 2018).

The high incidence of cancer in domestic animals is at least partially the result of strong directional selection that has led to inbreeding (Box 1) and/or evolutionary mismatches (Box 2). Indeed, cancer occurrence in domestic animals is often much higher than in humans or in their comparable wildlife ancestors. These high rates of cancer can result in special selective pressures. Then, by pleiotropy or through unique mutations related to domestication, selective pressure may lead to the odd unique solution to certain cancers, as shown below.

3 | ANTICANCER DEFENCES IN DOMESTICATED SPECIES

Compensation of a higher vulnerability to cancer through the selection of specific cancer defences occurs in various domesticated species, like pigs. Cutaneous melanoma is usually an aggressive form of skin cancer. However, in the melanoblastoma-bearing Libechov Minipig, tumours naturally regress without external influence (Bourneuf, 2017; Vincent-Naulleau et al., 2004). Spontaneous and complete tumour regression occurs in 96% of pigs (even at the metastatic stage), six months after birth, and are characterized by tumour flattening, tumour drying and depigmentation (Vincent-Naulleau et al., 2004). In calves, spontaneous regression of congenital cutaneous hemangiomas has also been observed (Priestnall, Bellis, Bond, Alony-Gilboa, & Summers, 2010). From an evolutionary point of view, two nonmutually exclusive processes could explain this phenomenon. Due to the inherited nature of this cancer, the domestication process has likely retained hosts able to mount strong anticancer defences as a compensatory response, and/or those bearing the inherited oncogenic mutations yielding to less aggressive forms of melanoma. While the first hypothesis seems to be verified in pigs, that is with the host's immune system playing a major role in eradicating melanoma cells (Kalialis, Drzewiecki, & Klyver, 2009), the second hypothesis is yet to be rigorously tested. Although genetic risk loci for osteosarcoma development have been identified in the cohorts of three large dog breeds (Greyhound, Irish Wolfhound and Rottweiler) (Karlsson et al., 2013; Zapata et al., 2019), a previous study showed evidence of spontaneous regression occurring in four large dogs (> 40kg): an Irish Setter, a spayed mixed-breed dog, a Golden Retriever and a Rottweiler (Mehl et al., 2001), also potentially supporting the first hypothesis.

The ancestor of domesticated hens could have potentially lived for 20–30 years and produced and incubated a small number of fertile eggs during a restricted period of the year. In contrast, strong artificial selection in the domesticated jungle fowl hen has resulted in a short lifespan and prolific, daily ovulation and egg laying, culminating in the high frequency of ovarian cancer occurrence in this species (Johnson & Giles, 2013). The physiological sequelae associated with ovulation, that is inflammation that produces potentially mutagenic pro-oxidants and pro-inflammatory molecules, has been proposed as the underlying mechanism initiating malignant ovarian cancer in chickens. Hens, as young as two years of age (Johnson & Giles, 2013), and 30%–35% of birds older than three and a half years (mostly hens in research facilities as commercial hens are removed from the flock by age two) are susceptible (Fredrickson, 1987). Interestingly, a five-fold variability between strains exists in the incidence of the disease (Johnson & Giles, 2006). Although genetic differences in cancer susceptibility between the strains cannot be excluded, since the strains derive from a similar genetic background, the subsequent evolution of anticancer responses in certain strains may be proposed.

Grey horses, especially those aged 15 years and over (up to 80%), develop spontaneous melanomas without the influence of UV radiation. These dermal melanomas primarily develop under the tail root, in the genital regions and on the eyelids and lips (Seltenhammer et al., 2004). In contrast to humans, these melanomas are encapsulated and the metastatic process is retarded and/or inhibited by unknown factors (Fleury et al., 2000).

In species that have been selectively bred for mammary gland growth and milk production (dairy cows and goats), there is a surprisingly low occurrence of mammary tumours, in contrast to domestic carnivores (Munson & Moresco, 2007). At the onset of lactation, strong inhibition of gene expression in pathways that are involved in cell proliferation (i.e. cyclins, cell division cycle-associated proteins and proteins involved in DNA replication and chromosome organization) were observed in the bovine mammary gland (Finucane,

Box 1 Genetic factors that promote cancer in domestic animals, creating an environment for the evolution of unique anticancer adaptations

The impact of domestication bottlenecks on genetic variation

Bottlenecks, strong artificial selection and small founder population size (reduced effective population size) during domestication have had the unintentional effect of attenuating genetic diversity and increasing inbreeding, resulting in the accumulation of deleterious genetic variants (higher genetic load). Favouring certain haplotypes contributes to genetic erosion and increased likelihood of homozygosity, coupled with higher frequency of long stretches of consecutive homozygous genotypes in the genome (ROH: runs of homozygosity) (Szpiech et al., 2013). ROH disproportionately harbour more deleterious homozygotes than other parts of the genome, and the presence of identical pathogenic variants of both alleles can give rise to recessive disorders (Assié, LaFramboise, Platzer, & Eng, 2008; Hosking et al., 2010). Thus, the impacts of deleterious homozygous mutations are magnified through inbreeding (Szpiech et al., 2013).

Mutations associated with favoured traits are not purged

Harmful mutations, which are generally purged from small wild populations (Charlier et al., 2016; Hosking et al., 2010), can rise in anthropogenic environments with artificial selection (Kimura, Maruyama, & Crow, 1963) as the selective pressure that they experienced in the wild becomes relaxed, allowing the frequency of nonsynonymous mutations to rise. If these mutations are associated with favoured phenotypes, humans will override the purging effect of nature and positively select for these traits (Bosse, Megens, Derks, Cara, & Groenen, 2019). In addition, if the detrimental variants are in linkage disequilibrium (LD) with the favoured allele that is strongly selected for (e.g. coat colour, milk production etc.), the frequency of the deleterious allele is expected to rise (i.e. genetic hitchhiking) (Smith & Haigh, 1974), resulting in genomic regions under strong selection harbouring elevated numbers of damaging mutations (Charlesworth, 2006; Good & Desai, 2014). Artificial selection and reductions in effective population size could also drive the frequency of deleterious alleles even higher (e.g. in cattle during the domestication process Kim et al., 2013). In addition, genetic drift can affect and increase mutation load in smaller populations, as seen in dogs (Björnerfeldt, Webster, & Vilà, 2006; Cruz, Vilà, & Webster, 2008; Marsden et al., 2016) and horses (Schubert et al., 2014). Despite their varied phenotypic diversity, domestic rabbits, dogs and cats have significantly lower genetic diversity compared to their wild conspecifics (Carneiro et al., 2011; Cho et al., 2013; Marsden et al., 2016). A higher proportion of deleterious alleles in ROH have been observed in pigs, chicken (Bosse et al., 2019) and cattle (Curik, Ferenčaković, & Sölkner, 2014; Zhang, Guldbrandtsen, Bosse, Lund, & Sahana, 2015), and in a Norwegian dog breed, the Lundehund (Kettunen, Daverdin, Helfjord, & Berg, 2017).

The impact of inbreeding, deleterious alleles and mutational load on cancer risk in domesticated animals

Loss of genetic variation and high mutational load can directly and indirectly contribute to cancer development and progression (Ujvari et al., 2018). Homozygosity of certain low-penetrance germline cancer genes has been identified as an underlying factor of some human cancers, for example oesophageal, oral, lung, bladder and breast cancer and acute lymphocytic leukaemia (reviewed in Denic, Frampton, & Gary Nicholls, 2007). Germline gene polymorphisms of known oncogenes (e.g. BRCA1, BRCA2, MC1R, KIT, NRAS and RAD51) have been associated with predisposition to various types of cancers (i.e. melanoma, mammary cancer, osteosarcoma and histiocytic sarcoma) in dogs, cats, pigs and horses (Curik et al., 2000; Flisikowski et al., 2017; Rivera et al., 2009). Apart from oncogenes, mutations of tumour suppressor genes have been identified as underlying causes of breed-specific cancer predisposition in dogs (Schoenebeck & Ostrander, 2014). Inbreeding and low genetic diversity have also been associated with the increasing incidence of domestic ferret cancers (Gustafson et al., 2018).

Reduced genetic diversity and infections by cancer-causing pathogens

Indirect consequences of reduced genetic diversity in domesticated animals could manifest in their propensity to cancer-causing infectious aetiologies. Genetically depauperate populations have been shown to be more vulnerable to pathogen infections than genetically diverse ones (reviewed in King and Lively (2012)), and loss of genetic diversity, particularly at important immune gene loci, can expose species (including domestic) to infections by cancer-causing pathogens (Acevedo-Whitehouse & Cunningham, 2006; Ujvari & Belov, 2011). The notion of transmissibility of tumours, malignant transformations caused by infectious agents, predates to the nineteenth century, when the jaagsiekte lung carcinoma in sheep was known to be transmissible, yet the causative retrovirus, was only identified in 1983 (Verwoerd, Payne, York, & Myer, 1983). Rous sarcoma virus (Rous, 1979; Weiss & Vogt, 2011); equine infectious anaemia virus (Vallée, 1904), feline and bovine leukaemia viruses (Onions, 1985) are all underlying pathologies that cause malignant transformation in domestic species.

Box 2 Evolutionary mismatch between present and past environments, creating an environment for the evolution of unique anticancer adaptations

A significant proportion of human cancers are due to evolutionary mismatches as ecological conditions and lifestyles in modern societies have been reshaped, resulting in maladaptation with our inherent genetics: the latter profiles reflecting adaptations to earlier and very different environmental circumstances (Aktipis & Nesse, 2013; Greaves, 2015). One can also predict a negative relationship between the time since domestication and the amplitude of mismatches, since artificial selection during long-term domestication favours genetic changes allowing species to be better adapted to their novel phenotype and/or environmental conditions. We need to determine why mismatches persist in certain domesticated species.

Long-term artificial selection for size in dogs results in higher incidences of bone cancer in larger breeds compared to smaller ones (Nunney, 2013). This suggests that despite a long history of domestication, selection on genes responsible for height (and hence a larger number of cells) has not been accompanied by selection for more efficient cancer defences, as observed in wild species (e.g. Paul and Gwynn-Jones (2003); Abegglen et al. (2015); Svetec, Cridland, Zhao, and Begun (2016)). Perhaps cancer defence selection is a considerably slower process than size selection. Alternatively, one can suspect that priority has been given to selecting dogs of a large size, without selecting large dogs with higher cancer resistance.

Overcrowding and intensive husbandry, as well as transportation of many domesticated species can enhance the transmission and spread of cancer-causing pathogens. Examples include DNA viruses that cause a form of leukaemia in poultry (Marek's disease), pulmonary carcinoma (jaagsiekte) in sheep, and a retrovirus causing bovine leukaemia (a virus that can be spread via contact, milk, saliva or commercial exchanges between herds) (Madewell, 1981). Similarly, bringing a wild species like the house sparrow *Passer domesticus* into captivity can induce hyperinflammation (Martin, Kidd, Liebl, & Coon, 2011), which is also known to promote tumorigenesis.

Finally, lifestyle and environmental factors linked to cancer-related deaths in humans, including diet and smoking also affect animals. Passive smoking and urban pollution have been associated with cancer in dogs (Reif, Bruns, & Lower, 1998; Reif & Cohen, 1971). Although controversial, certain studies suggest a link between exposure to household chemicals, herbicides and/or pesticides and the development of cancer in pets (Backer, Coss, Wolkin, Flanders, & Reif, 2008; Garabrant & Philbert, 2002; Gavazza, Presciuttini, Barale, Lubas, & Gugliucci, 2001; Glickman, Schofer, McKee, Reif, & Goldschmidt, 1989; Takashima-Uebelhoer et al., 2012). Obesity is also becoming a growing problem in dogs and cats. Overindulgence and accumulation of excessive amounts of adipose tissue in the body can predispose our closest companions to a plethora of diseases, including neoplasia (mammary tumours and transitional cell carcinoma) (German, 2006). Cancer also occurs in domesticated species including sika deer and cattle when animals are kept under suboptimal conditions, such as grazing on forage where the carcinogenic bracken fern (*Pteridium aquilinum*) grows (Jarrett, McNeil, Grimshaw, Selman, & McIntyre, 1978; Kelly, Toolan, & Jahns, 2014; Potter & Baird, 2000).

Negative effects of enhanced reproduction due to selection, and suppressed reproduction in pets

Domestication has led to increased reproductive effort and efficiency in several species, that is reaching sexual maturity earlier, surviving and reproducing longer, more frequent cycles, altered ovulation and sperm production rates, being less selective for mates, larger litter size, lessened embryonic mortality, shortened duration of pregnancy and lactational anoestrus (Setchell, 1992). In contrast to their wild counterparts, domestic cattle and pigs show no seasonal effect on their reproduction, reach puberty earlier and have shorter gestation. Similarly, laboratory rodents reach puberty earlier and show delayed senescence, ultimately doubling their reproductive lifespan.

Increased reproductive effort and efficiency cannot be disassociated from prolonged and altered fluctuation of endogenous hormone levels, some of the critical underlying factors of malignant transformations. The study by El Etreby et al. (1980) found an association between endocrine imbalance (increased secretory activity of pituitary growth hormone cells, and depressed secretory activity of follicle-stimulating hormone-, luteinizing hormone- and thyrotrophin-producing cells) and canine mammary tumorigenesis (Schneider, Dorn, & Taylor, 1969). Spaying bitches at a young age reduces the risk of mammary gland cancers in dogs and cats, but interestingly, the frequency of prostate cancer is slightly higher in neutered male dogs (Dorn, Taylor, Schneider, Hibbard, & Klauber, 1968).

Reproduction is prevented in many domestic animals. As in humans (e.g. Whitaker, 2012), this results in a reproductive mismatch for domesticated animals, with females being exposed to prolonged high levels of progesterone without subsequent lactation (e.g. in canids), and/or to recurrent high peaks of oestrogen (e.g. felids) because waves of follicles undergo atresia (Munson & Moresco, 2007). Thus, human interference with breeding of domestic animals results in lifelong exposure to steroid hormones which are major risk factors for mammary cancer development.

McFadden, Bond, Kennelly, & Zhao, 2008). This suggests that anticancer mechanisms compensating for increased risks of malignancies (associated with enhanced lobular alveolar growth (Reed, Kutasovic, Lakhani, & Peter, 2015)) have potentially been concomitantly and/or subsequently selected for.

Notably, benign tumours are more common than malignant tumours in Syrian hamsters, one of the world's most inbred animals (laboratory colonies of Syrian hamsters have originated from a single breeding pair in the 1970s) (Fritzsche, Neumann, Nasdal, & Gattermann, 2006). While malignant tumours may develop in hormone-producing glands (adrenal glands, lymph nodes) or digestive system organs, only four per cent of hamsters suffer from cancer, indicating that this severe inbreeding may have contributed to selection for alleles and genetic regions that provide enhanced tumour suppression.

Lost in the dichotomy between higher cancer resistance and lower cancer virulence, it is possible that the domestication process selects for a higher tolerance to cancer. Even if it comes with non-neutral effects on vigour that would be fatal in the wild, domestication can favour animals that tolerate the presence of tumours, by repairing the damage in a way that keeps the body functioning. An intriguing example (supporting the idea that domestication can also domesticate malignant diseases and/or favour tolerant hosts), concerns two species of tumour-harbouring hydra (Domazet-Lošo et al., 2014), kept under laboratory conditions for many years. Because the budding rate is reduced in tumour-bearing individuals compared to healthy ones, individuals with tumours are outcompeted by healthy ones when experimentally maintained together, a result that is also likely to occur in the wild (Bosch personal communication). Laboratory settings provide the tumour-bearing hydra with conditions akin to a domestic environment (food ad libitum, stable environmental parameters and no competition with healthy individuals). Under these conditions, not only are the tumour-bearing polyps maintained through time, they also vertically transmit non-aggressive tumours (to daughter polyps), as aggressive ones kill the hosts and are not transmitted. This example supports the idea that under domestic conditions, providing an environment with relaxed selective pressure, such unique host–tumour relationships evolve that are unlikely to exist in the wild.

4 | CONCLUDING REMARKS

Malignancies, from their appearance more than half a billion year ago (Aktipis & Nesse, 2013), trigger the evolution of myriad anticancer defences in multicellular organisms (Casás-Selves & DeGregori, 2011; DeGregori, 2011). However, the evolution of these adaptations is constrained by the need to achieve maximal fitness under different environmental conditions. A diversity of factors and/or ecological contexts has the potential to exacerbate cancer risks in organisms and, in return, boost the evolution of anticancer defences. For instance, the enhanced cancer defence of apoptotic response in elephants (although not a domesticated species) may be related to the fact that the elephant genome contains 20 copies of the tumour suppressive gene TP53 (Abegglen et al., 2015). Organisms naturally or artificially exposed to environmental oncogenic factors can, sometimes rapidly, evolve specific adaptations to cope with pollutants and their adverse effects on fitness (Vittecoq et al., 2018).

The domestication process places animals in unprecedented ecological contexts in which cancer risks are exacerbated on the one hand, but classical selective pressures are relaxed on the other (predation, food limitation). It is theoretically predicted that anticancer defences could be qualitatively or quantitatively different compared to those in the wild. Enhanced anticancer defences, if any, are traditionally most efficient in young individuals (Greaves, 2007; Jacqueline et al., 2017) because longevity is not usually the trait targeted for by artificial selection in domestic animals. While this process contributes to maintaining higher rates of cancer in older domestic animals, it should not hide the fact that at younger ages, an absence of malignant problems should rely on more efficient anticancer mechanisms than in wild species.

Domestication is not just a model but rather an authentic evolutionary process, allowing us to explore how artificial selection has potentially shaped the evolution of original host–tumour relationships. This could be the beginning of novel treatment development to eliminate or better tolerate cancer. Thus, rather than merely viewing the rare instances of cancer tolerance and resistance in domestic animals as merely an oddity, and something to be ignored in the light of the high cancer incidences typical of domestic animals, we should make these the target of further study. Sharing information from experimental and epidemiological studies between the veterinary and human medical fields could result in major advances in the understanding of selected anticancer defences during the domestication process.

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DATA AVAILABILITY STATEMENT

We will not be archiving data because this manuscript does not have associated data.

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