Title: A Systematic Literature Review of Animal Assisted Interventions in Oncology (Part I): Methods and Results

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Abstract: Animal-assisted interventions (AAI) use human-animal interactions to positive effect in various contexts including cancer care. This systematic literature review is the first part of a two-part paper series focusing on the research methods and quantitative results of AAI studies in oncology. We find methodological consistency in the use of canines as therapy animals, in the types of high-risk patients excluded from studies, and in the infection precautions taken with therapy animals throughout cancer wards. The investigated patient endpoints are not significantly affected by AAI, with the exceptions of improvements in oxygen consumption, quality of life, depression, mood, and satisfaction with therapy. The AAI field in oncology has progressed significantly since its inception and has great potential to positively impact future patient outcomes. To advance the field, AAI research in oncology should consistently improve the methodological design of studies, report data more completely, and focus on the therapy animal's well-being.

Introduction

Cancer is the second leading cause of death globally. In 2018, 18.1 million people were newly diagnosed and 9.6 million individuals died from cancer around the world.[1] As with all potentially chronic diseases, a cancer diagnosis and the subsequent treatment do not only come with debilitating physical consequences but also with concomitant psychological distress. Several studies show that the psychological distress from cancer can cause significant problems with adherence to treatment and increase the risk of morbidity and mortality.[2–4] In cancer and other chronic conditions, if the patients are not treated in a holistic way, conditions can worsen due to diagnosis or treatment side effects in addition to the actual consequences of the disease. While important research is being targeted to the treatment and eradication of the disease, there is a continued need for intervention strategies to address psychological distress and cancer related side effects. The National Cancer Institute, under the United States' National Institutes of Health, recognizes complementary and alternative medicines as medical products and practices that are not part of standard medical care. Animal-assisted interventions (AAI) is one complementary treatment of recent interest and is defined as a patient interacting with an animal to improve psychological distress, cancer-related symptoms (e.g. pain), and quality of life.[5–7] AAI refers to a number of activities and is broadly synonymous with terms including pet therapy, animal facilitated therapy, equine assisted therapy, and canine assisted interactions. These interventions can be subdivided into two categories—animal-assisted activities and animal-assisted therapies—that are both relevant to patients with cancer.[5–7] Animal-assisted activities are typically a brief, "meet and greet" animal interaction that improves quality of life in a general sense—for example, students with high stress levels interacting with puppies during an exam week.[8] Animal-assisted therapy typically refers to animal interactions that are structured and deliberately intended to produce a certain clinical outcome—for example, breast cancer survivors riding horses in order to improve muscle quality.[9] While research efforts have generally shown it to be beneficial or neutral in effect on the patient, most of the evidence for AAI is qualitative, anecdotal or observational in nature and rigorous clinical research practices have yet to be widely applied to this work.[10–14] These problems stem from both lack of theoretical rigor underlying experimental design and inconsistent methodological execution across studies. Relatively little work is done on the effects of AAIs from the animal's perspective.[15–18] This is ethically relevant if, for example, alleviation of patient stress is necessarily accompanied by increased stress on the therapy animal. In order to better address these issues and validate AAI as a complementary medicine for cancer patients, the relevant animal-assisted interventions research must be thoroughly analyzed.

In this first part of a two-part systematic review of the literature, we focus on the use of quantitative measures to investigate the efficacy of AAIs in oncology. We also focus on the research methodologies used by

AAI researchers with special attention paid to participant selection, study design, and research outcomes for both participants and therapy animals. Our overarching goal is to explicate a solid methodological foundation for future work in the field of AAI for oncology patients in order to generate rigorous clinical research studies that lead to wider acceptance and implementation of AAIs. In general, the second paper focuses on the proposed mechanisms and theoretical frameworks underlying AAI study design.[19]

Systematic Review Methods

We conducted a systematic literature review, under the direction of a research librarian, that focused on various terms for both AAI (including animal facilitated interventions, pet therapy or equine assisted activities) and cancer (such as neoplasm or oncology). We conducted 3 intermittently spaced preliminary searches from December 2017 to June 2018 to clarify the scope of the field, determine the most relevant databases, draft inclusion criteria for the articles gathered, and refine terms for official boolean and MeSH searches. The official full literature search was conducted and replicated afterwards, gathering any document format from the "beginning of time" to July 31st, 2018. We interrogated the PubMed, Web of Science, Scopus, CAB abstracts, CINAHL, Google Scholar, and North Carolina State University, and University of North Carolina-Chapel Hill's library databases for results [**Figure 1**]. Search string inquiries included any permutation of "cancer" and "animal assisted intervention" (e.g. oncology AND pet therapy; cancer AND pet therapy; neoplasms AND animal facilitated therapy; or neoplasms AND animal assisted intervention). Permutations of search terms were found automatically using PubMed's Medical Subject Headings (MeSH) feature and manually entered in non-PubMed databases. These myriad database searches yielded 928 hits in total which were stored in a citation manager. We then used a deduplication software tool to reduce the results to 452 papers before sorting these again by hand for residual duplicates, culminating in 336 papers. From our preliminary searches, we excluded any papers with little to no potential to contribute to our intended discussion. Particularly, we removed results focused on non-cancer conditions such as autism or post-traumatic stress disorder, and results providing no experimental data but rather instructions on how to set up a hospital AAI program. Utilizing these criteria, a first pass reading of titles and abstracts reduced the 336 papers to 54 journal articles and other formats (such as dissertations or online press releases). We further eliminated all formats other than literature reviews, journal articles, conference papers, and dissertations as they all merely pointed to and summarized study results published elsewhere. A full reading of the remaining 49 articles for specific relevance to our review's topic sentence resulted in 32 relevant publications. In this context, relevance is defined as providing independent, novel data or summary information specifically dealing with the efficacy of AAI and its variants in oncology.
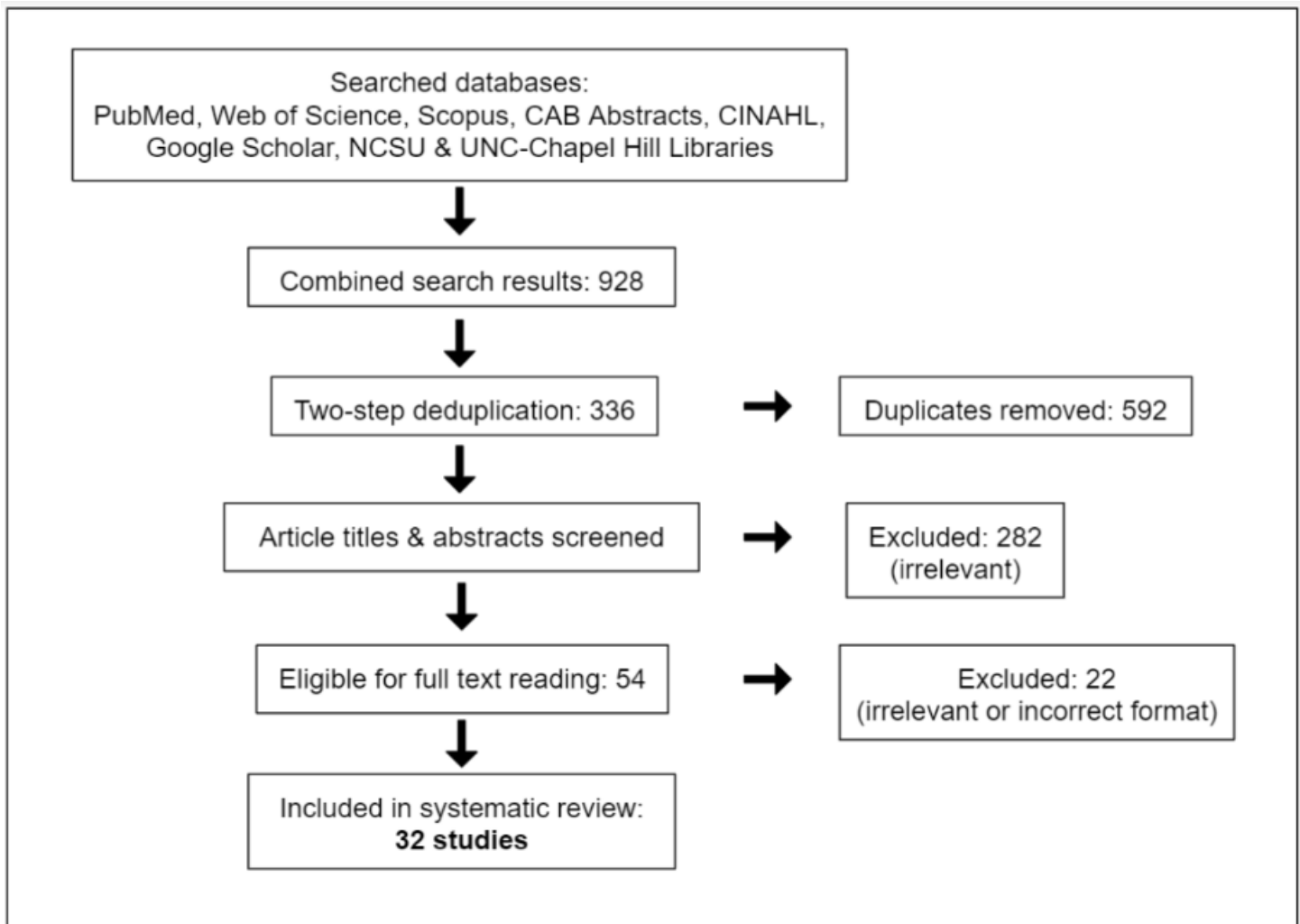
Fig 1. Flowchart summarizing the article selection process for this review.

Systematic Review Results and Discussion

Methods of AAI Studies in Oncology

Study Design: Participants

We first consider the study designs represented in the reviewed manuscripts. The work done in this section of the AAI field falls into three general categories: 1) systematic controlled trials; 2) observational studies with or without controls; and 3) broad, non-intervention surveys [**Table 1**]. In the systematic controlled trials category, the studies by Cerulli et al.[9], McCullough et al.[20], and McCullough et al.[21] compare intervention group effects to a control condition and randomly assign group membership. The second and largest research class is observational studies further consisting of quasi-experimental studies, pre- to post-intervention studies,

and medical case reports. Quasi-experimental studies often allow patients to self-select into the intervention group or simply assign membership using other factors such as recruitment date.[22–28] Pre- to post-intervention studies typically collect data before and after either each AAI session or the entire treatment regimen.[7,29–35] Some collect data only after the session or treatment is completed and many may also lack a control condition group.[36–43] Medical case reports deal with AAI's effect on one patient each and showcase dramatic effects on one patient that may be lost in summary statistics.[44,45] Both quasi-experimental and pre- to post-intervention studies can provide data suggesting efficacy and highlight potential mechanisms underlying AAI's benefits, while also capturing the subjective experiences of many participants. The third, non-intervention survey class is comprised of population surveys that investigate certain AAI stakeholders (e.g. hospital administrators or child life specialists) without actually subjecting the participants to an intervention directly.[46,47] These surveys of specific populations without intervention allow for closer analysis of attitudes, expectations and fears surrounding AAIs while also collecting important data on implementing such programs. The study designs reviewed can also be classified according to their subtype of AAI: animal-assisted activities (AAA) for studies generally improving quality of life and animal-assisted therapy (AAT) for studies targeted towards achieving a clinically relevant outcome.[8] Although the reviewed studies often claimed no label at all or adopted one of these two labels with varying degrees of accuracy, we used the aforementioned definitions to classify each study in **Table 1** for purposes of consistency. These classifications resulted in 13 AAA studies and 15 AAT studies with 3 falling into neither category.

Table 1 Study type and participant information for animal assisted intervention studies in oncology

Author & Year	Study Design; AAI Type	Sample Size	Age (in years)	Animal Type, Number & Breed
Aiba et al.[44]	Observational; AAT	1 patient	79	Dogs
Bibbo[41]	Observational; AAA	34 staff	--	Dogs
Bouchard et al.[36]	Observational; AAT	27 patients	r = 3-16	12 dogs
Buettner et al.[47]	Non-Intervention; Neither	75 patients & 5 relatives	m = 62.4; r = 18-87	Dogs
Caprilli and Messeri[43]	Observational; AAA	138 patients, 46 relatives & 52 staff	m = 3.5	4 dogs: 3 labradors (ages 3, 6 & 8) and a mixed-breed dog (age 5)
Cerulli et al.[9]	Randomized control trial; AAT	20 patients (control = 10)	m = 45.61	Horse
Chubak et al.[29]	Observational; AAA	19 staff	"pediatric"	Dog, Cats & Horses
Chubak et al.[46]	Non-Intervention; AAA	19 patients*	r = 7-25; m = 12.9 (SD = 3.6)	Dog
Coakley and Mahoney[27]	Observational; AAT	59 patients (non-/cancer patients unspecified)***	m = 59.56 (SD = 15.68); r = 24-88	Dog
Doobrow[58]	Non-Intervention; Neither	12 child life specialists	r = 18-45	Dog
Fleishman et al.[22]	quasi-experimental	37 patients	m = 57.2 (SD = 8.44)	Dog
Gagnon et al.[37]	Observational; AAT	16 patients, 16 relatives & 12 staff	89% between ages of 3 & 13	Dog
Ginex et al.[30]	Observational; AAT	100 patients (control = 50) + 41 staff	m = 55 (AFT) & 58 (control)	Dog
Haylock et al.[33]	Observational; AAA	20 patients	r = 21-79	Horse
Johnson et al.[23]	Observational; AAA	30 patients (human control = 10 & reading control = 10)	r = 25-27; median = 54	Dog
Johnson et al.[24]	Observational; AAT	30 patients	r = 39-77; median = 60	2 dogs: 1 long-haired daschund & 1 whippet
Kaminski et al.[25]	Observational; AAA	23 cancer*** & 47 other patients (control = 40)*	m = 9.86 (SD = 2.80)	Dog
Kumasaka et al.[31]	Observational; AAA	20 patients	m = 69.45 (SD =11.66) ; r = 43-83	Dogs, cats & rabbits
Larson et al.[49]	Non-Intervention; Neither	309 patients	r = 19-91; median = 59	Pets
Marcus et al.[38]	Observational; AAT	56 patients	m = 59.0 +/- 11.3	11 dogs: medium–large breeds and mixes**
McCullough et al.[20]	Randomized control trial; AAT	106 patients (control = 46)	r = 3-17 ; [Exp.: m = 8.9 (SD = 4.5)] ; [Con.: m = 8.1 (SD = 4.6)]	26 dog-handler teams
McCullough et al.[21]	Randomized control trial; AAT	26 therapy teams	r = 2-13	26 dogs: age r = 2-13; common breeds: golden retriever (17%), labrador retriever (13%), or mixes of these (16%)
Moreira et al.[39]	Observational; AAA	10 relatives & 6 staff	r = 4-6 (children), 20-45 (relatives) & 24-54 (nurses)	Dogs
Muschel[34]	Observational; AAT	15 patients	--	Dogs & Cats
Orlandi et al.[7]	Observational; AAA	178 patients (control = 89)	Experimental: m = 8.9 (SD = 4.5) & r = 25-83; Control: m = 8.1 (SD = 4.6) & r = 25-77.5	2 dogs: 1 border collie (age 8) & 1 Shetland sheepdog (age 9)
Petranek et al.[32]	Observational; AAA	9 patients	--	1 dog
Phung et al.[28]	Observational; AAA	128 patients (non-/cancer patients unspecified)***	18+	2 dogs: 1 young black labrador & 1 older giant cockapoo
Schmitz et al.[40]	Observational; AAT	47 cancer & 5 other patients; 2 handlers***	m = 63.3; r = 28-90; median = 65	2 dogs
Silva et al.[26]	Observational; AAT	24 patients & 24 staff	m = 8.58; r = 6-12	2 dogs: 1 Labarador retriever & 1 golden retreiver
Toro et al.[35]	Observational; AAT	15 patients	r = 3-15	Unspecified
White et al.[42]	Observational; AAT	8 patients	r = 39-61	1 dog: labradoodle (age 5)
Yom[45]	Observational; AAA	1 patient	54	1 dog: Bichon Frise/poodle (age 7)

Note: m = mean; r = range; SD = standard deviation; con = control; exp = experiment
* These studies also collected data from an unspecified number of relatives or staff.
** More detailed dog breed information provided in Marcus et al. 2014.
*** All studies focused on cancer patients only except for these 4 studies which had both cancer and non-cancer patients.

Inclusion and Exclusion Criteria

One restriction on participant selection in oncology populations is the exclusion of patients who have medical conditions that make the AAI either unsafe or difficult to complete (e.g. infection precaution or a recent invasive procedure), who were outside of the desired age ranges, who had an aversion or allergy to the chosen animal, or who couldn't complete the physical activities or psychological instruments of the study. Most studies also required the handler and therapy animal team to be certified by a reputable organization, to maintain general cleanliness protocols during AAI, to be up to date on vaccinations, and to submit to regular veterinary checks-ups. A few studies had additional study criteria worth considering. Bouchard et al.[48], Caprilli and Messeri[43], and Gagnon et al.[37] each excluded children unable to interact with a dog due to youth (e.g. breastfeeding babies) or cognitive disability. In other examples of unique criteria, some research groups required physician approval to participate in the study,[9,26,29] restricted entrant gender to focus on breast cancer in women,[33] or selected only participants with conditions requiring multiple hospital visits to ensure a longitudinal study.[42] Generally, AAI studies shared criteria protecting their participants and differed as needed for their research aims.

Age

The age range of each study's participants are detailed in **Table 1**. When provided, mean participant ages tended toward older adults (ages 55-75) or younger children (ages 3-12). Adolescent and young adults as well as middle-aged individuals appear to be underrepresented in AAI research with oncology patients. This research gap may result from difficulty recruiting oncology patients in these age ranges and future researchers should target these populations. Future work should also report detailed demographic information as AAI can have differential effects by subject age.[29]

Sample Size

Patient recruitment strategies included direct referral from medical staff, solicitation by email or fliers, and selection after reviewing medical records. Cerulli et al.[9], Larson et al.[49], and McCullough et al.[20] targeted statistically appropriate numbers of enrollees a priori, obtaining sample sizes of 106, 20 and 309, respectively. The remaining studies accepted all who met the inclusion criteria and ranged in sample size from 8[42] to 178[7] participants, excluding case reports and non-intervention surveys [**Table 1**]. While a study's number of participants may not be the sole cause of unsupported claims, future AAI work in oncology should aim to use statistical methods when determining the sample size that best provides high evidence for study outcomes.

Subject Type

An important aspect of AAI research design is deciding from whom to collect data as other stakeholders beyond the oncology patient may be in the treatment room. In total, 23 studies gathered data directly from

patients, 8 from parents, 10 from medical staff and 1 from animal-handler teams [**Table 1**]. Even though data collection from the subject of an intervention is paramount, these studies highlight the important perspectives of medical personnel and family members. In two special cases, Gagnon et al.[37] and Schmitz et al.[40] surveyed parents and handlers, respectively, as proxies for patients too young to provide useful research data. Generally, investigators note the potential of AAI to enhance relationships between patients, caregivers, and other family members, thus necessitating data collection from multiple stakeholders.

Animal Selection

Only 13 studies noted the breed, temperament or number of animals employed in their program; each of these included dogs in their research [**Table 1**]. The most common dog breeds employed were Labrador retrievers and mixes (7 studies), Golden retrievers and mixes (3 studies) and other mixes including neither Labradors nor Golden retrievers (4 studies). AAI studies in oncology generally did not indicate exclusion of therapy animals of any species based on temperament (aside from what would be required for a dog to become certified). With the exception of Ginex et al.[30], the few canine studies with temperamental preferences opted for calm dogs, hypothesizing that the dogs' mellowness would be beneficial to AAI outcomes. One equine study did specify the use of horses who were calm and gentle.[33] The number of dogs included in studies ranged from 1 for the case reports with one patient[29,49] to 26 dogs for the McCullough et al.[21] study. This study included 60 intervention group participants—even though the largest intervention group serviced 89 participants with 2 dogs.[18] These results indicate that human sample size does not always determine the number of animals needed in an AAI study. Parameters like longer study durations and fewer visits per patient per week, for example, can allow small numbers of animal-handler teams to service large intervention groups. Researchers should take number, breed and temperamental information into account when selecting animals and designing studies for optimal AAI outcomes.

Study Design: Parameters

Controls

Only 9 of the 32 studies used some form of control condition in their work. McCullough et al.[20] randomly assigned children to control or experimental groups but allowed brief interactions between control condition participants and therapy teams when unavoidable (i.e. in waiting rooms or hallways). In Ginex et al.[30], the investigators observed early in the study that participants in rooms with multiple beds presented practical and ethical concerns for using a control group and altered their design away from a randomized controlled trial. The researchers shifted to a sequential design with data collection from the normal care control group occurring during a specified time block of several weeks before that of the intervention group. Kaminski et al.[25] also abandoned their initial random group assignment strategy. Since their AAI sessions occurred once weekly, these

researchers included pet visitation day study recruits in the intervention group and placed recruits from all other days in the control group. Noting that friendly human interactions may be a source of AAI's benefits,[50,51] both the Johnson et al.[23] and Johnson et al.[24] studies used two controls—a reading group and a friendly human group—to isolate the dogs' effects on AAI outcomes. Orlandi and colleagues set up one chemotherapy treatment room with AAI and another without, creating intervention and control groups through participant self-selection.[7] This solution is a modified version of the sequential control group design and risks similar self-selection bias in results. Since the intervention group must travel to horse interaction centers for the physical benefits of equine assisted therapy, Cerulli and colleagues avoided cross-contamination concerns by instructing the control group to stay home and avoid new formal exercise programs.[9] Most pre- to post-intervention or quasi–experimental studies used the research participants as their own controls. All of these studies highlight the difficulties and considerations researchers deal with when designing AAI research for oncology patients and present some alternative control group strategies to address challenges in this research area.

Intervention location and sample type

On the question of intervention group sample type (i.e. individual vs. group) and the environment for the intervention, the results in AAI for oncology are mixed [**Table 2**]. For individual AAI sessions, 9 studies conducted the intervention in the patient's hospital room while 4 others moved patients to a designated private space. While only one research cohort used a multi-bed hospital room for group AAI sessions, 9 studies used a designated group space and 4 others hosted sessions in a common waiting area where the therapy animal interacted with all present. Future work should consider examining the effects of group versus individual AAI protocols as patient-animal interaction times can vary and because concomitant dealings with other humans present may further impact outcomes further. Relatedly, conducting AAI in a patient's hospital room may be more convenient than bringing him to a different private room. However, designated therapy spaces could provide a useful change of scenery and potentially eliminate negative influences of the patient's hospital room.

Table 2 Study design information for animal assisted intervention studies in oncology

Author & Year	Session Duration	Frequency	Study Duration	Intervention Type	Intervention Location
Aiba et al.[44]	15 mins	4/wk on weeks 1, 3, 5 & 6; 16 total	–	Individual	–
Bibbo[41]	Unspecified (dogs worked 20-90 mins/visit)	3/wk; 12 total	4 weeks	Individual	group & waiting rooms
Bouchard et al.[36]	8 hours	--	12 months	Individual	private room
Buettner et al.[47]	--	--	–	–	waiting room
Caprilli and Messeri[43]	2 hours	1/wk	6 months	Group	group room
Cerulli et al.[9]	1 hour	2/wk; 32 total	–	Individual	horse stables
Chubak et al.[29]	Unspecified (dogs worked 1-2 hours)	Various	–	Both	private & waiting rooms
Chubak et al.[46]	20 mins	1	5 months	Individual	private room
Coakley and Mahoney[27]	10 mins	1	3 years (Sep. 2004- Jul. 2007)	Individual	private room
Doobrow[58]	--	--	–	–	–
Fleishman et al.[22]	m = 15 mins	m = 18 per patient	–	Individual	private, group & waiting rooms
Gagnon et al.[37]	8-16 hours	1+ (multiple visits = 44%)	12 months	Individual	private room
Ginex et al.[30]	--	4/wk	–	Individual	multi-bed room
Haylock et al.[33]	--	--	9 months	Group	horse stables
Johnson et al.[23]	15 mins	1	–	Individual	private room
Johnson et al.[24]	15 mins	3/wk; 12 total	–	Individual	private room
Kaminski et al.[25]	90 mins	1/wk	–	Group	group room
Kumasaka et al.[31]	30 mins	1/mo; (25% had multiple visits)	2 years	Group	–
Larson et al.[49]	--	--	–	–	–
Marcus et al.[38]	10-15 mins	1+	6 months (Jan. 2012- Jun. 2012)	Individual	–
McCullough et al.[20]	m = 24 mins	1/wk; (sessions per child: m = 10.2 & SD = 3.1)	–	Individual	semi-/private rooms
McCullough et al.[21]	m = 24 mins	1/wk	–	Individual	semi-/private rooms
Moreira et al.[39]	1 hour	--	4 months (Oct. 2014- Feb. 2015)	Group	group room
Muschel[34]	1.5 hours	1/wk; 10 total	–	Individual	–
Orlandi et al.[7]	60 mins	1	6 months (Nov. 2005- Apr. 2006)	Group	group room
Petranek et al.[32]	10-20 mins	1	Experiment Ongoing	Individual	–
Phung et al.[28]	5-10 mins	1	–	Individual	private room
Schmitz et al.[40]	m = 32.7 mins (median = 30 mins & range = 10–67 mins)	m = 1.6/wk per patient; median = 1/wk	11 months (Jun. 2014- May 2015)	Individual	private & group rooms
Silva et al.[26]	30 mins	3+ in 4 weeks	20 months (Jun. 2015- Jan. 2017)	Group	–
Toro et al.[35]	--	--	1 month	Individual	–
White et al.[42]	Unspecified (post-interview: r = 20-60 mins)	3+	–	Individual	private room
Yom[45]	--	2+	–	Individual	private room

Note: m = mean; r = range; mins = minutes; wk = weeks; mo = months

Duration and Frequency

There was a large degree of variation in duration and frequency of AAI between studies, with a high potential to impact the outcomes. The studies' animal-assisted interventions range in frequency from 1 session (10 studies) to 32 sessions (1 study) and in duration from around 10 mins (5 studies) to 8-16 hours (1 study) [**Table 2**]. AAI studies in oncology have had total study durations ranging from 1 month to 3 years. There are no clear patterns within the duration and frequency data. However, researchers using 10 or more sessions per patient often pointedly classify their work as AAT, implying an intention to produce a certain clinical outcome. The link between frequency and effectiveness of AAI nevertheless remains unclear and future research efforts should address this.[27]

Structured vs. Unstructured Sessions

Beyond session duration and frequency, the majority of studies indicated that participants were free to interact with therapy animals as they wished. However, five studies either moderately or strictly structured their participants' animal interactions. Both Muschel[34] and Schmitz et al.[40] divided their semi-structured sessions into three blocks of broad activities such as watching or being introduced to the dog, physically playing with or holding the dog, and arranging for another therapy session. Since Silva et al.[26] is a group animal interaction study, a set of activities from a predefined list were chosen for each session based on group interests and dynamics. Both strictly structured session designs were for equine assisted therapy modalities and typical activities included phases of acclimation or bonding, grooming, riding, and education about horses.[9,33] Structuring AAI sessions ensures a high level of treatment fidelity and reproducibility while permitting researchers and medical staff to better contend with factors such as limited space, patient mobility issues, and infection protocols. Unstructured interactions allow for greater treatment flexibility as participants can choose the level of engagement best for them (e.g. playing with a puppy quietly, talking to a therapy horse, or watching a dog perform command tricks.)

The study designs found in AAI oncology studies represent a broad range of rigor and theoretical usefulness while adapting to various constraints. While there are well-founded scientific standards and conventions for research design, hopefully this discussion can be a guide to those trying to discern what type of study will best help them investigate their questions of interest about AAI in oncology and pet therapy more broadly.

Results of AAI Studies in Oncology

Physiological Endpoints

Since most studies investigated multiple endpoints, often with differing results, this section discusses the efficacy of AAI in oncology according to the physiological or psychological endpoints of interest. This section also discusses trends in each endpoint's results and the devices used for collecting the relevant data.

Heart Rate

The most researched physiological parameter is heart rate with the six relevant papers showing no consistent trends in results [**Table 3**].[7,9,20,25–27] Coakley and Mahoney[27] and Silva et al.[26] saw no significant changes in heart rate. Even though they recorded heart rate throughout riding sessions and pre- to post-treatment, Cerulli et al.[9] used their heart rate data only to help calculate oxygen saturation maximums in patients (discussed later), noting that a rider's heart rate and oxygen consumption varies with the horse's gait. Kaminski et al.[25] noted significantly higher heart rates in their study's intervention group both before and after therapy but no significant changes within either the experimental or control groups. The uniformly higher experimental group heart rates are attributed to an anticipatory effect of receiving AAI, to not monitoring heart rate continuously during sessions, and to the more physically interactive nature of the intervention compared to control activities (e.g. reading, puzzles or video games). Kaminski et al.[25] also mention that their study did not include a reaction to a stressful event as other studies showing decreased heart rate do. However, Orlandi et al.[7] also did not include a stressful event, and they note a significant heart rate decrease in both the experimental and control groups; they attribute this and all other positive results to the increased attention the study's participants received from medical staff. In McCullough et al.[20], the experimental group has significantly higher heart rates after intervention compared to before. The investigators suggest that this is a product of AAI encouraging physical activity in participants. They also maintain that, while statistically significant, these results are not clinically significant and may indicate increased engagement as opposed to an AAI stress response. When obtaining heart rate, standard hospital methods—like counting radial pulse[27]—are used by most with two exceptions.[7,20,25,27] Cerulli et al.[9] collected heart rate data using a Polar Electro Inc. heart rate monitor during exercise measurements and Team System recorder belts from Finland's Polar during horse riding sessions. Silva et al.[26] used age-specific BP3ABOH-G-Tech semi-automatic pressure meters throughout their heart rate data collection. The results of studies on heart rate appear to depend somewhat on the nature of the intervention, ranging from vigorous physical activity[9] to more passively interacting with the animal.[7] Analysis of heart rate variability can shed light on the emotional states of both humans and canines.[52] As such, future quantification of this variable could benefit from 1) its noise-free, reliable and continuous recording during interventions; 2)

assessment of non-AAI baseline heart rates for those in experimental groups; and 3) careful annotation of activities pursued during AAI therapy sessions.

Table 3 Results of animal assisted intervention studies in oncology

Author & Year	Psychological Endpoints	Physiological Endpoints	Other Endpoints
Aiba et al.[44]	--	--	--
Bibbo[41]	Staff note AAI helped patient QoL	--	Pet Attitude: staff AAI approval = 8.24 (scale of 1-9) & prior perceptions impacted PE
Bouchard et al.[36]	--	--	--
Buettner et al.[47]	--	--	--
Caprilli and Messeri[43]	PE: 94% of parents & 96% of staff noted AAI helped children	--	Behavioral Coding [SAM: most children very happy with dog & normal/very happy without ; Behavioral scales: child-animal intearction and child awareness = above average & child-environment ineteraction = average]
Cerulli et al.[9]	QoL: ↑↑↑	O2Sat.: ↑↑↑ ; Muscle Strength: ↑↑↑	--
Chubak et al.[29]	--	--	--
Chubak et al.[46]	Distress: ↓↓↓ ; Anxiety: ↓↓↓ ; Depression: ↓↓↓ ; Pain: ↓↓↓ ; Anger: ↓ ; PE: majority of staff & children noted AAI helped	--	Behavioral Coding [Patient and parent behaviors = generally positive; common acts = dog tricks or handler interactions]
Coakley and Mahoney[27]	Mood: ↑↑↑ ; Pain Level: ↓ ; Energy Level: ↑ ; Hostility: ↓↓↓	HR: <> ; BP: <> ; RR: ↓↓↓ ;	Pet Ownership: 47.5% (uncorrelated with other data)
Doobrow[58]	--	--	--
Fleishman et al.[22]	QoL(well-being): [social: ↑↑↑, functional and physical: ↓↓↓ & emotional: <>] ; Satisfaction: [psychological aspects = high & physiological aspects = neutral]	--	Pet attitude: patient affinity for animals = 6.08 (high; range of 1 to 7)
Gagnon et al.[37]	--	--	--
Ginex et al.[30]	Anxiety: ↓↓↓ (in both groups) ; Depression: ↓ ; Energy Level: ↓↓↓	--	--
Haylock et al.[33]	QoL: <>	--	--
Johnson et al.[23]	PE: Both dog group & friendly human group noted AAI helped	--	Group pet ownership: dog = 50%; human = 70%; reading = 50%; (uncorrelated with other data)
Johnson et al.[24]	Mood: <> ; Anxiety: ↓ (for all groups) ; PH: <> ; PE: 50% (Dog Group), 90% (Friendly Human Group) & 60% (Reading Group) note AAI helped	--	--
Kaminski et al.[25]	Mood: ↑ (in both groups)	HR: ↑↑↑ ; Cortisol: ↓ (in both groups)	Behavioral Coding [Time showing positive affect: 46% (exp.) & 19% (con.) ; Time showing neutral affect: 53% (exp.) & 81% (con.) ; Time showing positive touching: 57% (exp.) & N/A (con.)]
Kumasaka et al.[31]	--	--	Pet attitude: 80% interested in & 70% liked pets ; Pet ownership: 95%
Larson et al.[49]	--	--	Pet ownership: 55%
Marcus et al.[38]	PE: 98.2% of respondents welcome another AAI visit	--	Pet Ownership: 50% (currently) & 34% (previously) ; Pet attitude: 80% liked dogs & 11% liked cats ; (both uncorrelated with other data)
McCullough et al.[20]	Anxiety: ↓↓↓ (in both groups) ; QoL: <>	HR: ↑↑↑ ; BP: ↑↑↑	Behavioral Coding [Common acts with dog: petting (92%), talking (69%) & photos (32%)] ; Pet Ownership: 67%
McCullough et al.[21]	--	Cortisol: <>*	Dog Behavioral Coding [Mean behaviors/session: 9.14 (affiliative), 9.69 (stress) & 0 (high stress) ; Most coded behaviors/session: oral behaviors (4.52), lip licking (2.31) & tail wagging (1.98) ; stress and affiliative behaviors correlated significantly]
Moreira et al.[39]	--	--	--
Muschel[34]	--	--	--

Table 3 Results of animal assisted intervention studies in oncology (continued)

Author & Year	Psychological Endpoints	Physiological Endpoints	Other Endpoints
Orlandi et al.[7]	Anxiety: ↓↓↓ (in both groups) ; Depression: ↓↓↓ (in exp group) ; Anger: ↓↓↓ (in both groups)	HR: ↓↓↓ (in both groups) ; BP: ↓↓↓ (in both groups) ; O2Sat.: ↑↑↑ (in exp group) & ↓ (in control group)	--
Petranek et al.[32]	QoL: ↑	--	--
Phung et al.[28]	Anxiety: ↓↓↓ ; Pain level: ↓↓↓ ; Energy Level: ↑↑↑ ; PE: 94% note AAI helped	--	--
Schmitz et al.[40]	--	--	Qualitative Content Analysis [most common act: "stroking the therapy dog" ; most common emotion = "pleasure"] ; Pet ownership: 33% (currently; dogs = 82%) & 33% (previously)]
Silva et al.[26]	Distress: ↓↓↓ ; Anxiety: ↓↓↓ ; Depression: ↓ ; Pain Level: ↓↓↓ ; QoL: <>	HR: <> ; BP: <>	--
Toro et al.[35]	--	--	--
White et al.[42]	--	--	Pet attitude: 100% dog lovers ; Pet ownership: several participants previously owned pets
Yom[45]	--	--	--

Note: <> = no significant change; ↑ = increase; ↑↑↑ = significant increase; ↓ = decrease; ↓↓↓ = significant decrease; m = mean; r = range;
con = control; exp = experiment; N/A = Not Applicable
QoL= quality of Life; PE= perceived effectiveness; PH= self-perceived health; HR= heart rate; BP=blood pressure; RR= respiration rate;
O2Sat= oxygen saturation
* McCullough et al. 2018b measured canine salivary cortisol.

Blood Pressure and Respiration Rate

The second most researched physiological parameter is blood pressure, with the same heart rate studies —excepting Cerulli et al.[9]—also looking at this measure [**Table 3**].[7,20,25–27] The majority of these studies saw no significant changes in blood pressure (75%)[20,26,27] or did not specify the result of blood pressure measurements (25%).[25] Orlandi et al.[7] alone noted a significant decrease in blood pressure for both control and experimental groups matching that of their heart rate result. Blood pressure data were collected by sphygmomanometer cuff and stethoscope,[20,27] Dinamap or other standard hospital device[7,20,25] or using BP3ABOH-G-Tech semi-automatic pressure meters from G-Tech Scientific Limited (Hong Kong).[26]

Respiration rate—a measure related to both heart rate and blood pressure— was only studied by Coakley and Mahoney.[27] By counting inhalations and expirations for a minute, these researchers observed a significant decrease in respiration rate. Little more can be said for blood pressure or respiration rate in response to AAI for oncology but, similar to patient heart rate, further research is warranted. This is especially true as Orlandi et al.[7], Coakley and Mahoney[27], and other studies have seen significant decreases in these parameters with AAI. Regarding physiological monitoring devices, it is clear that researchers in this field could benefit from utilizing more precise methods and, potentially, real-time monitoring systems before, during and after animal-assisted interventions for tracking these three parameters.

Cortisol

Measuring cortisol is the gold standard of stress detection but, as the analyte must be taken from urine, blood, or saliva, serial measurement during an AAI protocol is troublesome.[53–55] This may explain why monitoring of cortisol levels is not more common in AAI oncology studies. Kaminski et al.[25] observed non-significant decreases in salivary cortisol for both the experimental and control groups from a similar pre-AAI starting point. Their collection methodology utilized sterile cups first stored in a freezer before bulk processing in a hospital laboratory. However, the authors also mention that roughly half of their collected pre- and post-therapy samples were lost to evaporation during long-term storage, restricting their data set. McCullough et al.[20] also looked at therapy dog salivary cortisol across five medical institutions with AAI programs. Using equipment and analysis provided by Salimetrics LLC (California, USA), these researchers found no change in the dogs' cortisol concentrations with intervention duration, session frequency, or number of people present during the AAI. Overall, McCullough and colleagues' work suggests that therapy dogs are not significantly stressed during AAI. Further human studies of AAI's effects on cortisol should pair larger sample sizes with careful attention to when and how often cortisol is collected during the research process. McCullough et al.[20] also note that future cortisol work with dogs should utilize additional animal-focused stress measures to investigate certain behaviors (like yawning or panting) that may alleviate or indicate dog stress otherwise missed in pre- to post-intervention collections of analytes.

Other Physiological Endpoints

Cerulli et al.[9] looked at Body Mass Index, principal muscle group strength, and maximal oxygen consumption before and after 16 weeks of equine assisted therapy in breast cancer survivors. Only the intervention group saw significant improvements in any of the three categories with average maximal oxygen consumption notably increasing by 28.29%. The authors maintain that these equine assisted therapy results are similar to those of other physical activity studies with breast cancer survivors. Cerulli and colleagues measured Body Mass Index using a portable bioelectrical impedance device (Handy 3000; DS Medica, Milano, Italy) and captured muscle group strength by attaching inertial measurement devices (Free-Power; Sensorize, Rome, Italy) to resistance training equipment. They also estimated maximal oxygen consumption using heart rate and the Astrand–Rhyming cycle ergometer test on a model 839E Monark bike from Monark Exercise AB (Sverige, Sweden). While their collection methodology is less clear, Orlandi et al.[7] also note a significant increase in experimental group oxygen saturation while that of the control group decreased, though not significantly. These studies suggest a potential improvement in oxygen consumption over time regardless of AAI therapy animal or session activity level.

Psychological Endpoints and Quantitative Surveys

Negative Emotional States

Several studies investigated AAI's effect on negative emotional states, generally finding significant decreases in anxiety and stress after AAI [**Table 3**]. Depression-focused instruments show both reduction and no change.[7,20,24,26–30] Several studies investigating anxiety with a control condition saw a decrease in both control and experimental groups individually post-intervention, but no significant difference between groups.[7,20,30] Chubak et al.[29] results were bifurcated by age with participants under 13 years old experiencing a greater improvement in effect than older patients. Silva et al.[26], Coakley and Mahoney[27], Kaminski et al.[25], and Orlandi et al.[7] showed a significant decrease in depression and improvement in mood—the latter only in the control condition—but Ginex et al.[30] and Johnson et al.[24] saw no change in depressive state for any group.[7,24–27,30] The authors of McCullough et al.[20] were especially surprised by the lack of a significant difference in negative emotion between the control and experimental groups of their longitudinal study. They posited that the modest reductions observed were still consistent with previous work showing stress decreases as pediatric oncology treatment progresses. The only overall increase in stress was observed in the parents of participants in the McCullough et al.[20] study. Here, the stress metrics of the intervention group's parents were slightly lower than the stress of control group parents. None of the studies investigating depression, stress or anxiety used the same psychological instruments as any other except for Johnson et al.[24] and Coakley and Mahoney[27] who both used versions of the Profile of Mood States. Overall, these results indicate that AAI generally affects mood states neutrally or positively even if much more investigation is needed to fully clarify these effects.

A few studies also investigated AAI's effect on anger, hostility and aggressiveness using quantitative surveys.[7,24,26,27,29] Silva et al.[26], Johnson et al.[24], and Chubak et al.[29] found no significant change in hostility before and after their interventions, using the Brunel Mood Scale, the Profile of Mood States and the PedsQL Present Functioning Scales, respectively.[24,26,29] Both Johnson et al.[24] and Silva et al.[26] noted that small sample sizes were likely the cause of the lack of statistical significance for their findings. Two studies showed significant decreases in hostility and anger for both control and experimental groups.[7,27] With a version of the Profile of Mood States, Coakley et al.[27] observed significant improvements in anger and "many patients called the experience rewarding, happy, very pleasurable, comforting,'' among other positive comments. Orlandi et al.[7] found a significant reduction in aggressiveness for their pet therapy group when administering the A.De.Ss.O test (Anxiety, DEpression, Somatic Symptoms, hOstility), a reduced version of other Symptom Questionnaires.[56,57] However, these researchers also proposed that their pet therapy intervention had little effects on aggression as they noticed a similarly significant reduction in aggression for the control group. Overall, animal-assisted interventions appear to have a neutral or positive affect on anger, hostility and aggressiveness in oncology patients.

Other Psychological Endpoints

A few studies evaluated parameters beyond negative emotional affect, some finding consistent decreases in perceived pain levels with AAI [**Table 3**].[26–28] However, investigations into fatigue and energy levels vary, with Coakley and Mahoney[27] and Phung et al.[28] finding increases in subject energy while Ginex et al.[30] found significant decreases in energy within, but not between their study's experimental and control groups.[27,28,30] While the duration of Ginex et al.[30]'s interventions are unclear, both Coakley and Mahoney[27] and Phung et al.[28] had extremely short interventions of 10 minutes or less which may explain the increased energy in their participants due to the novel burst of canine interaction. Regardless, the relationship between energy levels and AAI is ripe for further investigation. No study used the same instruments to assess subject fatigue or pain but there was some preference for Likert-type face scales when determining pain levels when determining pain levels in children.

Quality of Life and Self-Perceived Health

Six AAI studies in oncology investigated the effects of AAI therapy on quality of life [**Table 3**].[9,20,22,26,32,33] Most of these studies found no significant differences after AAI, but Cerulli et al.[9] noted an increase in quality of life in their equine assisted therapy participants. This unique result may be due to Cerulli and colleagues working only with women whose cancer was in remission for at least 6 months, ensuring the absence of underlying conditions related to cancer that could significantly affect quality of life measures. Fleishman et al.[22] only observed emotional well-being increases when the researchers controlled for concomitant physical well-being decreases. Preliminary analysis of Petranek et al.[32]'s work shows an improvement in long-term life outlook after participants receive a single art and AAI session. McCullough et al.[20] and Petranek et al.[32] used the PedsQLTM and QOL-C30/BN20 surveys, respectively, to evaluate cancer patient quality of life while the remaining studies used versions of the Functional Assessment of Chronic Illness Therapy (FACIT) system.[9,22,33]

Considering the self-perceived health of participants, Johnson et al.[23] developed an AAI-specific instrument but found no statistically significant correlation between dog visits and self-perceived health. Surveying based on topics from Johnson et al.[23]'s instrument, the medical staff in Bibbo[41] agreed that animal-assisted activities should continue and was helpful for their patients' self-perceived health. All of these studies indicate that quality of life and self-perceived health are neutrally or positively affected by animal-assisted interventions.

Perceived Effectiveness

Many researchers also investigated the perceived effectiveness of AAI using survey questions unique to each study.[22–24,26,28,29,38,43] Those investigating this parameter found most all of their participants and other stakeholders were satisfied with the therapy implemented and AAI more broadly. Some participants would even

recommend AAI to others in the hospital.[26,38] Ginex et al.[30] descriptively analyzed open-ended responses from patients and staff, finding that AAI provided three improvements: a sense of happiness or hopefulness, a distraction, and the motivation necessary for recovery. While it is not quantitative data, many AAI studies in oncology also list quotes expressing gratitude to further demonstrate participant satisfaction with AAI. On the whole, perceived effectiveness and satisfaction with AAI therapy is the most positive and the most robustly supported result in AAI oncology studies.

Pet Attitudes

Many AAI researchers in oncology asked about pet ownership and attitudes towards pets in order to evaluate the effect these variables had on intervention outcomes. Current and past pet ownership ranged from 47.5%[27] to 95%[31] of a study's participants but largely had no correlation with or effect on specific AAI outcomes when compared to non-pet owners [**Table 3**].[20,23,27,31,38,40,42] Similarly, attitudes towards animals were generally positive with no effect on the measured parameters, excepting the medical staff in Bibbo[41] whose previous opinions of AAI affected their perception of its effectiveness.[22,31,38,41,42]

Behavioral and Qualitative Coding

Video-based Coding

Beyond physiological measurement and psychological surveys, visual data collection methodology coupled with behavioral coding predominates in AAI studies in oncology [**Table 3**].[20,21,25,29,40,43] During AAI sessions, Kaminski et al.[25] recorded video for the first 2 minutes, at 10 minutes, and again at 20 minutes before three investigators coded the percentage of time the child displayed different types of affect, time spent on interactive tasks, and amount of touching. When analyzing the video segments, they found children in the intervention group displayed significantly more positive affect, more touching, and less neutral affect than those in the control condition. Researchers in McCullough et al.[20] also video recorded their AAI sessions, noting that pediatric patients mainly petted (92% of sessions), talked to (69%), and looked at pictures of therapy dogs (32%). A related study also recorded the dog's behaviors during AAI sessions with two cameras and a 26-point ethogram developed by the study's researchers and animal behavior professionals.[20] Coding behaviors as affiliative, moderate stress, and high stress, McCullough and colleagues found that equal numbers of moderate stress responses were recorded in each session with no canine displaying any high stress behaviors. Expanding these results, dogs who displayed more stress behaviors also displayed more affiliative behaviors in the same session. McCullough and colleagues showed evidence supportive of cortisol measurement in AAI studies, finding a direct correlation between salivary cortisol levels and displays of stress behaviors in dogs.[20]

Observational Coding

In Chubak et al.[29], a research assistant used a semi-structured form to record all the behaviors of and interactions between the dog and the patient. These researchers found that both patients and parents generally displayed positively coded behaviors throughout, with the most commonly noted interactions being those between the handler and patients, parents or therapy dogs (i.e. dog doing a command trick or handler talking to the parent or patient.) Schmitz et al.[40] coupled retrospective analysis with handlers' post-hoc write-ups of AAI sessions. These investigators found that pleasure was the most often perceived emotional response, and that the dog enhanced both patient communication and relaxation. Caprilli and Messeri[43] assessed AAI's effects with independent observers present during the session, with the self-assessment manikin pictorial assessment, and with analysis of participating children's graphic productions. Showing active engagement in the animal-assisted intervention, the behavioral scales completed by observers scored the participants near average in child-environment interactions and above average in both child-animal interaction and level of awareness. Results from the self-assessment manikin showed pediatric participants to be very happy with the dog and normal or very happy without it. Finally, of the 77 children's drawings —thought to be representative of their emotions and feelings— 56% were animal drawings, confirming the participants' interest in the dogs' presence on the ward. Although all videos recorded were only displayed as art pieces and no definitive results were provided, Petranek et al.[32] also took pictures of patients' faces before and after treatment to demonstrate AAI's effects. Despite the fact that Petranek and colleagues' judgements of the improvement showcased by these photos are necessarily subjective, this research method may be a new source of evidence for AAI's benefits in oncology if coupled with objective image analysis.

Overall, the results of various behavioral coding techniques in AAI studies in oncology show that the most common AAI activity is touching or grooming, that dogs are not visibly highly stressed by AAI, and that patients have generally positive experiences interacting with therapy animals.

Non-intervention Survey Studies

Four studies met this review's inclusion criteria but did not report results of an AAI experiment directly.[46,47,49,58] Asking a convenience sample of oncology patients over 4 days, Buettner et al.[47] found that most people read (60%), talk to others (20%), play phone games (5.3%) or engage in other activities while awaiting treatment, and that anxiety level strongly predicted participants' willingness to participate in AAI. The survey responses indicate that providing communication opportunities (93%), mental engagement (92.3%) and a means to pass time (88.8%) would be the main benefits of an AAI program if implemented. Chubak et al.[46] surveyed the top 19 pediatric oncology hospitals with ongoing AAI programs, noting that little is understood about the implementation of animal-assisted activities beyond pilot studies and single-site efforts. Focusing on safety, effectiveness and study design, they found that 1) all programs included dogs, while cats and miniature

horses were included at one hospital each; 2) most activities took place in outpatient waiting rooms, individual patient rooms, play rooms or hallways; and 3) eleven sites allowed pediatric oncology patients to participate in animal-assisted activities—with one hospital only allowing those cleared under infection control protocols to be involved. Of the sites permitting animal-assisted activities for pediatric oncology, all allowed petting of the animal and for the animal to sit on the child's bed with a barrier. In Chubak et al.[46] results, many hospitals also allowed group visits and some even allowed feeding and brushing of the therapy animal. Overall, these investigators conclude that several top hospitals had successfully integrated AAI into their oncology treatment programs by employing strict training certifications, cleanliness protocols, and participant exclusion criteria. In her work, Doobrow[58] assessed child life specialists' perceptions of AAI's benefits for pediatric oncology patients, arguing that this population is especially vulnerable to stress, anxiety, and the treatment side effects of oncology. Utilizing the 12 respondents from an online survey distributed in early 2015, Doobrow[58] found that 11 thought animal-assisted therapy was generally useful for pediatric oncology, but only 6 believed animal-assisted therapy could be used during treatment procedures. As with Chubak et al.[46] survey, Doobrow also found that dogs were the default therapy animal and that the most common interactions were petting, holding and talking to the therapy animal. In 2009, Larson and colleagues asked 309 tertiary care oncology patients whether they had serious concerns about posthumous care for their pets and if their pets had helped during their oncology treatment.[49] They found that only a small segment of the whole group (4%) and of pet owners (7%) desired more information on pet care resources, obviating the need for further action. However, Larson and colleagues also found that 45% of the 170 respondents with pets noted they felt healthier because of their pet and 48% of this group also said their pets helped them deal with stress associated with their diagnosis. In summary, these non-intervention studies compiled important information on patients' interest in, how hospitals currently implement, and how the relevant medical staff perceive AAI programs, while also ensuring that chronically ill patients have fewer unmet pet-care needs.

Conclusions and Research Outlook

Limitations of the State of the Art

In their critical literature reviews, Stern et al.[11] and Chur-Hansen et al.[14] laid out important methodological changes that could improve our understanding and increase the scientific validity of animal-assisted interventions. These suggestions included tracking patient and staff attitudes towards animals, randomizing participant group assignments, comparing pets familiar to the patient versus unfamiliar animals, isolating the animal as the crucial experimental variable, ensuring inter-rater reliability for behavioral and

qualitative content coding, and noting times between intervention sessions and survey completion or physical data collection for pre- to post-intervention type studies. Although the field of AAI in oncology has progressed significantly since these publications, we discuss additional limitations and general areas of improvement in this section.

   As noted previously, researchers use either self-generated questionnaires—which are not always independently validated and can bias results—or existing psychological instruments, but rarely the same survey for the same endpoints across studies. While there are many constraining barriers such as language, age, and study endpoints that justify a different or new instrument, consistent psychological instruments would greatly improve the ability to compare results. Study focus represents a similar field limitation in that AAI researchers are not looking for a common set of generalizable outcomes that systematically advance the state of the art.[11] This lack of study focus consensus also creates issues with data recording and protocol reporting as individual studies may not collect information relevant to the field generally. For example, details such as the number and type of dogs included or the duration and frequency of interventions, if not reported, can severely weaken a result's generalizability.

   Addressing a different issue, some researchers note when animal-assisted interventions are occurring during treatment (e.g. before radiation therapy, after surgery, six months post-treatment, or in the first 4 weeks of diagnosis) while others neglect to do so.[9,24,30] For example, Coakley and Mahoney[27] collected patient data both at the beginning of their hospitalization and while others were getting ready for discharge, suggesting that they may have observed stronger effects if all participants received AAI at the peak of their illness. Both Johnson et al.[24] and McCullough et al.[20] explicitly note that severity of cancer symptoms or type of treatment can affect how researchers should interpret study results. Not tracking these variances in disease or treatment progression makes results very difficult to directly compare across studies, generating an aura of one-off studies rather than repeatable, reliable work. Recruiting patients for AAI also presents a challenge as most studies do not control for either the self-selection of dog-lovers to participate or for the respondents to be those with the most exaggerated experiences, positive or negative.[31] Other papers struggle to account for or completely ignore the potential effects that handlers, parents and other people in the room could have on results.[59] Johnson et al.[24] also note that cross-contamination of members in experimental and control groups when in waiting or treatment rooms could affect results.

   Research efforts could benefit greatly from longer recording periods and real-time, continuous monitoring of participants. These would provide information on the long-term effects of AAI and on which activities lead directly to which physiological or behavioral responses. For example, a pilot study published by Foster et al.[60] used custom wearable systems on both human and canine participants to evaluate the effects of a brief clinical AAI. The system presented in this work collected data for the entire intervention duration that,

theoretically, could be directly correlated with specific session activities post-hoc. Novel work is on the horizon; Nardo et al.[61] describe efforts to decrease cortisol collection times for dogs, which would allow this variable to be measured more efficiently. Also, Aoki et al.[62] describe an effort to measure AAI's effects on brain activity with near-infrared spectroscopy. These novel techniques may also bolster the amount of detailed information provided by AAI studies.[61,63] The AAI field in oncology also does not closely track other concurrent interventions and complementary medical treatments (e.g. psychological counseling, acupuncture, or therapeutic touch) that could affect long-term AAI results. For example, McCullough et al.[20] explicitly state that they did not collect data on covariates or other comorbidities that could have affected the endpoints of interest. Aiba et al.[44] and Fleishman et al.[22] are notable exceptions and both track other medical treatments coinciding with their study interventions. However, these researchers mention that they are only interested in measuring a "common complementary therapy option as it readily occurs in these settings" rather than in completely isolating the animal-assisted interaction's effects.

In relation to self-reported data, Bibbo[41] discussed the Hawthorne effect, where subjects modify behavior when aware of their being observed. While it was not a significant factor in that work, the AAI field in oncology should seek ways to control or eliminate this potentiality. For various reasons, many studies excluded participants who could still benefit from a complementary or alternative medical therapy similar to AAI without the concomitant risks and complications (e.g. zoonotic infection risks, aversion to dogs or allergic reactions to cats). Future research efforts should explore the use of modified protocols, hypoallergenic animals, robotic pets, and even remote animal interaction set-ups in order to reach these excluded populations.[64,65] Several studies mentioned that larger sample sizes would have provided better results and more noticeable effect sizes.[22–24,27,40,47,58] Like McCullough et al.[20] and Larson et al.[49], future researchers should perform a priori statistical analyses of the sample sizes and other numeric parameters needed to provide robust data about the AAI phenomenon of interest. Finally, while most researchers allowed for unstructured interactions with therapy animals, future studies should also implement reasonably structured sets of activities in order to investigate which produce the greatest effects and to evaluate the merits of structured sessions.

The animal-assisted intervention field also has non-methodological limitations that can affect experimentation and results. The first is the field's general imprecision in the use of terms. Many others have noted that animal-assisted activities (AAA), animal-assisted interventions (AAI), animal-assisted therapy (AAT), animal-facilitated therapy (AFT), pet therapy and all of the variations with "canine" or "equine" inserted throughout are used sporadically, interchangeably, and non-specifically despite some efforts to formalize the language in the field.[11,14,66–68] In creating **Table 1**, we experienced some difficulty when attempting to strictly re-classify the studies included in this review according to AAA or AAT as several articles did not provide sufficient information about the aims of their work. The article gathering portion of the

literature review process was also much more complex due to the myriad and inconsistent terms used as keywords for animal-assisted intervention studies. Even if these terms have slightly different meanings, the nuances ought to be fully elucidated and agreed upon to solidify the field's theoretical basis and facilitate better communication of results. Furthermore, as the field evolves so will the experimental and treatment goals of researchers, possibly making it necessary to further subdivide the terminology beyond AAA and AAT.

Another unique and persistently problematic limitation of the AAI field is the tendency to ignore the therapy animal's perspective and the potential effects that AAI can have on them. In oncology, only 4 of 32 AAI papers investigated any effect on the therapy animal[20,24,26,40] with one other paper briefly mentioning taking steps to ensure "therapy dogs did not show any signs of stress during the study."[43] Although most studies recruit from nationally recognized organizations, universal standards for human-animal interactions should always be followed and should include regular veterinary screenings and ensuring the constant presence of a professional knowledgeable about animal well-being.[5] Beyond the important ethical principle of doing no harm, the quality of care delivered can be significantly affected by both the mental and physical state of the participating animal. Similar to other subfields of AAI, oncology can be stressful and researchers should monitor the effects on the animal very closely. Currently, animal welfare is monitored largely either by pre- to post-intervention cortisol measurements or video analysis of canine stress behaviors, but additional methods of assessing this important component of AAI are worth exploring.[69]

AAI in oncology and the AAI field in general has a potential crucial limitation in the types of animals chosen. While there are good reasons for defaulting to dogs (e.g. many humans are already quite familiar with dogs, they are already well integrated into many hospitals, and they tend to have suitable temperaments for AAI), dogs are overrepresented—almost to the exclusion of any other live being—amongst animals employed in AAI. Assuming different animals have different characteristics, diversity in this area could broaden AAI's range of positive effects. This is well demonstrated in the equine assisted therapy papers where the authors note special benefits due to bonds formed while riding the horses; features understandably absent from the human-canine bond.[9,33] Speaking to patient preference, some participants in the Phung et al.[28] study requested that cats be used rather than dogs; welfare effects for cats would need to be closely monitored, however. Diversifying the animal pool within reason could also ameliorate the issues of excluding those humans who are allergic or have an aversion to dogs. Finally, studying animals other than dogs can better allow researchers to make broadly valid claims about animal-assisted interventions, rather than generalizing from one test animal to all other cases.

While many papers make a point to track infections and exclude those with fear of the chosen therapy animal, not much is understood about the potential negative effects of AAI for humans. Although initially hard to conceive, examples of negative AAI effects could include a subject's heart racing above safe levels or a subject suffering a deeper depression upon cessation of the AAI program and thus the loss of their new animal

friend. A version of the latter effect is implied by a terminal cancer patient in Muschel[34]: "I've always had animals in my life. I love them. But I don't want one now because I would want to take it home with me and I'm not going home." Coupled with the lack of focus on the dog (negative and positive outcomes), ignoring negative effects on humans could mean that researchers may only be getting part of the complete AAI picture; this is without even mentioning other stakeholders such as family or medical staff. A fair rejoinder is that most of the psychological instruments used are already sensitive to potential AAI downsides and that a simple discussion of their results is adequate to detect any negative psychological effects. However, we observe that this is truer in theory than in practice. When physiological or psychological results are aberrant or paradoxical, they are often not interpreted by researchers as negative consequences of AAI but rather attributed to other factors. When working with humans, hospitals and complex conditions like cancer, it is already sufficiently difficult to know which effects are direct outcomes of AAI. Thus, individual studies and the field as a whole could benefit from neutral experimental designs geared towards collecting potentially negative effects as well as positive outcomes. It is important to state that a reliable finding of negative aspects to AAI in oncology—for example, the well-known risk of infection—is not fatal to the field. Future participants can simply be advised of the risks and side effects of pet therapies before making a well-informed decision about this complementary treatment option.

There are too few high-quality studies to permit confident assertions about some effects of animal-assisted interventions on cancer patients. However, treatment with these complementary interventions can still be informed by the larger body of evidence supporting positive effects for medical animal-assisted interventions or non-clinical human-animal interactions more generally. For example, although the results of studies mentioned in this review were mixed, a meta-analysis conducted by Waite et al.[70] found AAI can effectively result in "large changes in pain, distress, and anxiety."

This Review's Limitations

While we endeavored to provide a comprehensive picture of quantitative measures used for investigating the efficacy of AAIs in oncology, our systematic literature review has implicit and explicit limitations. Although our inclusion and exclusion criteria were based on several preliminary searches, it is possible that, due to our definitions and keywords, a relevant article was excluded or an unrepresentative article included. To illustrate this point, studies meeting the "oncology" criterion had to explicitly list at least one patient in the study who was diagnosed with cancer. However, large AAI studies may exist that included cancer patients without explicitly providing a list of participant medical conditions. Alternately, in some included studies, cancer did not constitute all or even a majority of the participants' diagnoses.[25,27,28,40] This latter issue especially may decrease some of the specificity that the included results have when assessing AAI's efficacy in

oncology. Additionally, while we did not exclude papers based on country of origin, limiting the reviewed articles to those published in English (or with English translations) may have effectively had this disparate outcome. We are aware of three potentially relevant papers, one from Konigorski et al.[71], Andreu et al.[72], and Borgatti et al.[73], that were excluded for linguistic reasons. Another limitation of this work is that we did not conduct a formal risk of bias analysis for each paper included in or excluded from this review.[74] While many of the papers assumed AAI would benefit cancer patients and interpreted their results on the strength of this assumption, steps to mitigate bias were generally undertaken, information was presented objectively, and "the believability of the link between exposure and outcome" was not fundamentally compromised. This work also aims to use AAI in oncology as a lens to better understand the human-animal bond more broadly. However, some results are not generalizable to all other AAI cases with or without cancer. For example, the overwhelming majority of the cited AAI studies in oncology use dogs only, introducing the possibility that the results summarized are more representative of canine assisted interventions than AAI as a whole. While we can make certain pronouncements based on the research reviewed herein, those conclusions may not be applicable to other human-animal bonds (e.g. bonds with military dogs or bonds with race horses) or even to other kinds of animal-assisted interventions (e.g. AAI for post-traumatic stress disorder or AAI for autism).

Summary and Conclusion

Here we presented the results of a systematic literature review evaluating the designs and efficacy of animal-assisted intervention studies in oncology through quantitative metrics. We found that researchers have little to no consistency across experimental methodologies other than preferring temperamentally calm dogs to be therapy animals, excluding extremely high risk patients, and enforcing practical hygienic standards for therapy teams. Most studies were observational and employed pre- to post-intervention or quasi-experimental study designs, however a few researchers conducted randomized controlled trials. Studies often investigated groups at the extremes of the age spectrum with adolescents, young adults, and middle-aged populations being underserved. Most studies preferred either individual or group AAI sessions comprised of unstructured activities and we found no patterns in the session durations and frequencies used across studies.

The results of these studies in oncology showed that animal-assisted interventions generally have a neutral, sometimes positive, effect on the physiological and psychological endpoints of interest. Specifically, oxygen saturation increased, quality of life improved, perceived satisfaction with AAI was high, and depression and other negative mood states decreased among research participants. Most, if not all, other variables—both physiological (e.g. heart rate, blood pressure, respiration rate, and cortisol) and psychological (e.g. anxiety, distress, hostility, self-perceived health, and quality of life)—investigated across studies showed no significant changes with AAI. In some studies, behavioral coding from recorded videos and direct observation showed that

stroking the therapy animal was the most common affiliative session behavior and that the animals involved displayed no or few high stress behaviors. Patients, relatives and medical staff all generally viewed AAI as helpful in oncology and a majority would recommend or welcome future animal visits. Many of the aforementioned stakeholders held positive opinions of animals or owned pets at some time, though neither parameter correlated with any other study data. As a therapeutic modality, the observed benefits of AAI are likely to be context dependent. If true, this would necessitate the personalization of animal-assisted treatments to individual patients and environments in order to elicit the positive outcomes desired.[28] As the effects of certain therapy animals, intervention procedures, and treatment environments are better understood for cancer patients and communication amongst researchers in the field continues to increase, an authoritative modular protocol may be possible. This would permit medical staff to take or leave the components that meet their patients' needs while preserving validity and comparability across published studies. Improved data reporting (e.g. tracking comorbidities,) unification of field terminology, and attentiveness to therapy animal well-being are additional suggestions that can greatly advance the state of the art.

The second part of this two-paper systematic literature review focuses on the mechanisms and theoretical frameworks proposed by researchers in oncological AAI. The detailed discussion herein seeks to be a guide for researchers investigating the topic of AAI in oncology and animal therapies more broadly. In time, animal assisted interventions will be a well-validated complementary treatment, with greater understanding of the impact on patient health and well-being.

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