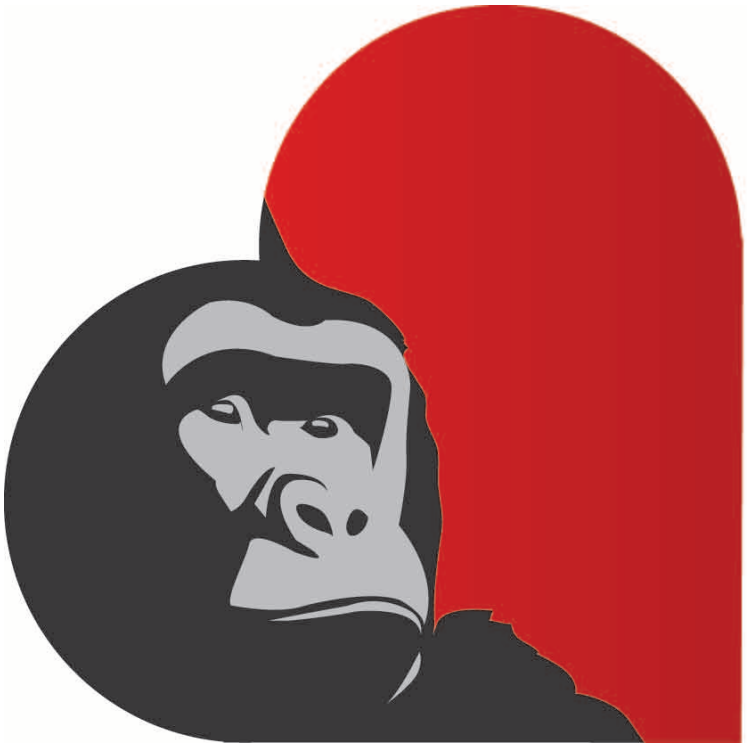

THE GREAT APE HEART PROJECT

A Collaboration to Understand Heart Disease, Reduce Mortality and Improve Cardiac Health in all Four Great Ape Taxa

www.greatapeheartproject.org

2012 White Paper

The Great Ape Heart Project (GAHP): a Collaboration to Understand Heart Disease, Reduce Mortality and Improve Cardiac Health in all Four Great Ape Taxa

ABSTRACT

Cardiovascular disease (CVD) has been identified as a major cause of death in captive great apes [gorillas (*Gorilla gorilla*), orangutans (*Pongo pygmaeus, Pongo. abelii*), chimpanzees (*Pan troglodytes*), and bonobos (*Pan paniscus*)]. The goal of the Great Ape Heart Project (GAHP) is to design an innovative and coordinated national program to investigate ape CVD and establish uniform, state of the art, cardiac diagnosis, and treatment and prevention strategies for great ape CVD. A 2010 Institute of Museum and Library Services National Leadership Collaborative Planning Grant (IMLS-NLG) funded a Planning Workshop that brought together a targeted audience of cardiac and ape specialists from the zoo, academic, laboratory animal, clinical practice, and research communities in February 2011. The workshop was professionally facilitated by Dr. Onnie Byers of the Conservation Breeding Specialist Group (CBSG). The workshop participants assessed currently available resources, identified needs and impediments to progress, and agreed on specific actions to be taken in four areas of ape CVD: Clinical Diagnosis/Treatment, Pathology, Identifying Etiology, and Communication. As a result of the planning meeting, the Association of Zoos and Aquariums (AZA) management groups for all four ape taxa have now agreed to support the efforts of the GAHP in standardizing and optimizing data collection.

In order to practice exemplary stewardship of captive ape collections, AZA professionals must understand what factors are similar, or different, within and across the four ape taxa. Currently, there is incomplete understanding of how to diagnose, treat and monitor affected apes, and how to adapt techniques which are used to address heart disease in humans and domestic animals, to apes. The Workshop confirmed that significant impediments to the zoological community's ability to manage ape CVD included a lack of standardized data collection across taxa, no comprehensive searchable ape-wide clinical and pathological database, and a lack of dedicated research in the areas of etiology, diagnostics, and treatment modalities.

INTRODUCTION

Cardiovascular disease (CVD) has been identified as a major cause of death in captive great apes [gorillas (*Gorilla gorilla*), orangutans (*Pongo pygmaeus, P. abelii*), chimpanzees (*Pan troglodytes*), and bonobos (*Pan paniscus*)]. Currently, there is incomplete understanding of how to diagnose, treat and monitor affected apes, and how to adapt techniques which are used to address heart disease in humans and domestic animals, to apes. In order to address ape CVD and practice exemplary stewardship of captive ape collections, Association of Zoos and Aquariums (AZA) professionals must understand what factors are similar, or different, within and across the four ape taxa. The goal of the Great Ape Heart Project (GAHP) is to design an innovative and coordinated national program to investigate ape CVD and establish uniform, state of the art, cardiac diagnosis, and treatment and prevention strategies for great ape CVD. An Institute of Museum and Library Services (IMLS) one-year National Leadership Collaborative Planning grant (IMLS-NLG) was obtained, ensuring adequate funding to bring together a targeted audience to participate in actively planning a strategic approach for solving this problem. In February 2011, an IMLS-NLG funded GAHP Planning Workshop, which was facilitated by the Conservation Breeding Specialist Group, brought together cardiac and ape specialists from the zoo, academic, laboratory animal, clinical practice, and research communities. This professionally-facilitated meeting assessed currently available resources, identified needs and impediments to progress, and agreed on specific actions to be taken in four areas of ape CVD: Clinical Diagnosis/Treatment, Pathology, Identifying Etiology, and Communication. The overriding aim of this strategic planning workshop was to establish clinical, and pathologic, cardiac diagnostic and treatment guidelines in all four great ape species that describe how to efficiently manage, reduce and prevent heart disease in these endangered and charismatic animals.

1. Strengths of this project include: Enabling a cooperative effort among holders of great apes that reduces competition for resources and maximizes the use of data across all institutions and researchers.
2. Developing a strategy that will give veterinarians and their consultants' access to species-wide reference values for cardiac ultrasound measurements, and clinical pathologic values for advanced serologic tests (such as cardiac biomarkers) in all four species.
3. Creating a network of Subject Matter Experts (SME) that will be available to provide practical, real-time directives to their colleagues in how to standardize and evaluate examinations, so that species-specific, standard measurements can be derived.

Zoo Atlanta's partners for this National Leadership Collaborative Planning grant were Cleveland Metroparks Zoo and the Emerging Diseases Research Group of the University of Georgia College of Veterinary Medicine.

Background

Cardiovascular disease is a major cause of mortality in all four great ape taxa managed in captivity with anecdotal press reports and published journal articles describing ape deaths due to cardiac disease dating back to the mid-20th century (Manning, 1942). Mortality reviews of captive apes have reported that CVD is a significant cause of death in 41% of gorillas (Meehan et al., 1994), 20% of orangutans (Lowenstine et al., 2008), 38% of zoo chimpanzees (Backues et al., 2008), and 45% of bonobos (Clyde, unpublished data). The histological pattern most commonly seen in apes during postmortem examinations (Schulman, 1995) differs from the common atherosclerotic coronary artery disease ("fatty plaques") pattern seen in humans (Varki, 2009, Lowenstine & McManamon 2012) and from CVD patterns seen in domesticated animal species. While heart disease is expected to affect geriatric animals within most populations, it is of great concern that it is also being documented as a cause of premature deaths in young apes. It is not only a threat to the individual animals but it also may negatively impact the genetic variability necessary for sustaining a viable captive population.

The potential incidence of heart disease in wild ape populations is not yet entirely attainable due to the limited post mortem data available on free ranging species of apes. The best post mortem database in wild apes is that of the Mountain Gorilla Veterinary Project, which includes more than 100 cases of mountain gorillas (*Gorilla gorilla beringei*) and 5 Grauer's Eastern Lowland gorillas (*Gorilla beringei graueri*) (unpublished, Lowenstine 2011). Another study (Terio et al. 2011) details 11 post mortem examination in common chimpanzees of the *schweinfurthii* subspecies (*Pan troglodytes schweinfurthii)*. In the mountain gorillas, the prevalence of heart disease is 4% and includes infections, and valvular and fibrosing cardiomyopathy. In an isolated population of Grauer's gorillas under severe pressure from surrounding human activities, both of the adult males examined so far had severe myocardial lesions and enlarged hearts contributing to death.

Increasing sophistication and technological advances in the detection, clinical and pathologic understanding, diagnosis, treatment and monitoring protocols for heart disease in human and veterinary medicine, have been dramatic over the past few decades. Similarly, there has been exponential growth in our understanding of early patterns and underlying pathogenesis of human heart disease, and the development of detailed serologic cardiac biomarker assays such as B-type naturietic protein, troponins, and microRNA assays in humans and some domestic animals (Vasan, 2006).

There exists a critical need to investigate and understand cardiovascular disease in all four great ape species. However, our understanding of the underlying mechanisms of ape heart disease, and our ability to establish an effective approach to diagnose, treat and monitor ape heart disease, has historically been limited.

Management of great apes in AZA accredited zoos is coordinated through Species Survival Plans (SSPs); great apes SSPs are organized within an Ape Taxon Advisory Group (TAG). SSP and TAG advisors volunteer their time to establish husbandry guidelines and medical standards. Individual animal records are kept locally, with CVD-relevant clinical and pathologic data collected in a non-standardized manner. Unfortunately, our understanding of the underlying mechanisms of ape CVD, and our ability to establish an effective approach to diagnose, treat and monitor ape heart disease, has historically been limited by several factors. These include:

1. No centralized mechanism for data coordination and sharing;
2. No standardization in antemortem diagnostic tests and treatments or postmortem procedures;
3. No mechanism to connect clinical data with postmortem findings;
4. No mechanism to ensure confidentiality and security when managing such sensitive data;
5. No sophisticated database tool to identify where disease patterns are similar or different within and among the different ape taxa;
6. A consistent lack of dedicated resources and personnel.

These limitations prevent critical retrospective and prospective investigations to examine ape CVD and impede ape management groups from forming alliances with SMEs.

Grant-Funded Activities

In 2010, IMLS awarded Zoo Atlanta a one-year National Leadership Collaborative Planning grant (IMLS-NLG). This funding supported the establishment of the Great Ape Heart Project (GAHP). Grant partners were Zoo Atlanta, Cleveland Metroparks Zoo, and the Emerging Diseases Research Group of the University of Georgia- College of Veterinary Medicine (UGA-CVM), working with key collaborator Linda Lowenstine (UC Davis College of Veterinary Medicine).

Activity One: Full-time Project Coordinator .The first planning grant activity was to hire a full-time Project Coordinator, based at Zoo Atlanta, to assist partners by facilitating communication, handling routine inquiries for resources or referral to SMEs, and planning and executing grant-funded meetings.

Activity two: Executive Steering Committee. As part of the IMLS-NLG, in November 2010 a 19-member GAHP Executive Steering Committee, representing numerous regional and national organizations and with 100% representation from all AZA ape management groups (animal managers, veterinary clinical and pathology advisors), and targeted SMEs, met at Zoo Atlanta.

During the Executive Committee meeting, the following topics were identified as being key areas of focus in a GAHP IMLS-NLG Planning Workshop to be held in February 2011.

1. *Data coordination and sharing between institutions and communities interested in ape CVD.* A coordinated strategy for standardizing cardiac examination techniques, reporting, or analyzing cardiac data, in any ape species except gorillas does not exist.
    a. At the time, diagnostic and treatment strategies for zoo animals relied on individual veterinarians, often working with consulting human and veterinary specialists within their local communities.
    b. Examination parameters (equipment, technique, data collected) were often determined locally, and the data collected is stored and interpreted individually.
    c. Efficiency and accuracy of diagnostic analysis was highly influenced by the experience level of the individual specialist(s) with that species.
2. *A lack of species-appropriate reference values, and/or limited access to existing data, makes diagnosis and treatment difficult.* The lack of a centralized medical database where data can be collected, stored, and analyzed was seen as a critical issue.

a. The current zoo-wide medical animal recordkeeping software (MedARKS) does not provide a way to compare cardiac data across institutions or species within a taxonomic group.
b. Developing species-specific cardiovascular anatomical and functional physiological reference ranges for "normal" versus "abnormal" cardiac examinations for all four ape species was a critical need.
c. In November 2010, the Gorilla Cardiac Database has data just on gorillas but similar data are limited, anecdotal, or entirely lacking in orangutans, chimpanzees, and bonobos.
d. Early efforts within the laboratory community have produced some early data on chimpanzees, but additional study and correlation with larger number of affected apes is needed (Lammey et al, 2008).
e. Collection and analysis of such data (as with the Gorilla Cardiac Project) is an enormous task, which requires coordination, funding and dedicated personnel.

3. *Correlation of postmortem examination findings with the antemortem clinical examination patterns seen in the apes has not been done.*
    a. Such clinicopathologic examinations, discussions, and correlations, on a species-specific and taxonomic basis, might lead to improved diagnostic and prognostic decisions regarding which animals have adequate heart function and which treatment modality should be elected.
    b. There is also a need for coordination of pathological terminology between and among the ape species.
    c. There is a need for recruitment of and consultation with human medical cardiac pathologists, and for more rigorous and standardized pathologic correlation of the multi-organ complications of chronic cardiac disease in the ape species.

In Ssummary, the executive steering committee felt that there was a clear need for a standardized, coordinated consensus-based clinical and pathologic approach within and across each of the four ape taxa. It was also felt that a centralized, dedicated coordinator was needed to assist veterinarians and animal managers to access the available data, appropriate resources, and experienced Subject Matter Experts (SMEs). Such a system would allow individual zoo veterinarians and their consultants to maximize diagnostic and prognostic tools and treatments. This would, therefore, contribute to defining a "best-practice" approach to ape cardiac health.

Similarly, the small cadre of specialists who have developed some experience in a particular ape species, or have invested time across multiple ape species, are currently overwhelmed by the demand for their help, across and within species. These specialists volunteer tremendous amounts of time consulting on nationally-dispersed individual patients, or on orienting newly-recruited cardiologists, ultrasonographers, veterinarians and clinical pathology specialists across the country. While some consultation is expected and welcomed, the demand exceeds the time available from this small group of individuals.

Activity three: GAHP Planning Workshop. The IMLS-NLG funded GAHP Planning Workshop brought together stakeholders within AZA and non-AZA communities in order to review current resources, define needs, and establish action plans and priorities to address ape

CVD. Over three days, 52 workshop participants, representing 33 institutions, including veterinary clinicians and pathologists, DVM and MD cardiologists, geneticists, epidemiologists, nutritionists, animal managers, and other ape specialists from zoos, sanctuaries, universities and primate centers, met at Zoo Atlanta. This was an unprecedented gathering of SMEs from different backgrounds to work collaboratively in an effort to address great ape CVD. This professionally-facilitated meeting assessed currently available resources, identified needs and impediments to progress, and agreed on specific actions to be taken in four areas of ape CVD: Clinical Diagnosis/Treatment, Pathology, Identifying Etiology, and Communication. The Workshop confirmed that significant impediments to the zoological community's ability to manage ape CVD included a lack of standardized data collection across taxa, no comprehensive searchable ape-wide clinical and pathological database, and a lack of dedicated research in the areas of etiology, diagnostics, and treatment modalities.
Key subjects for discussion at this workshop were:

1. The need for a standardized, coordinated, consensus-based clinical and pathologic approach within and across each of the four ape taxa.
2. A coordinated data sharing system between institutions and communities interested in ape CVD.
3. Species-specific cardiovascular anatomical and physiological reference ranges were needed for cardiac examinations in all taxa except gorillas.
4. The need for a mechanism to correlate postmortem examination findings with antemortem clinical examination findings.
5. How to determine if this is one disease entity across the ape taxa, or a potential grouping of several disease syndromes.
6. How to use data generated to identify potential CVD etiologies.
7. The need for a centralized full-time person to manage the GAHP.

The workshop participants separated into the four working groups, (Etiology, Pathology, Clinical Diagnosis/Treatment, and Communications) and plenary sessions were held periodically throughout the three days. A professional facilitator ensured that the objectives for the workshop would be met through breakout and plenary sessions within and between four working groups. The groups were balanced to ensure a mix of participant expertise, Executive Committee members, and representation of all four ape taxa. At the end of the workshop, each of the working groups completed a document detailing their goals and the action items needed to achieve them (Appendix 1). Additionally, each action item was put into a timeline and assigned to a committee member.

Through the plenary discussions as well as the working group summaries, with additional input from the Executive Steering Committee meeting, the needs of the targeted audience were prioritized and out of these, 20 were voted on by the participants as the top priorities for immediate focus (Appendix 2). Out of these priorities, it was clear that creating a comprehensive database to allow cross-taxa CVD data input and analysis, maintained by a dedicated GAHP Manager, was an essential need that had to be accomplished before most other identified action items could be satisfied. For example, a few identified needs that depend on the establishment of a comprehensive database are:

1. To establish taxon-specific echocardiographic reference parameters needed to validate clinicopathologic diagnostic and treatment options for all four ape taxa.
2. To develop a comprehensive data set to provide the basis for future investigations and projects.
3. To develop a way to standardize and coordinate pathologic diagnoses with clinical syndromes.
4. To provide for an ongoing, sustainable resource for zoos to help in the management and stewardship of their living and deceased ape collections.
5. To determine if hypertension, diet or genetics play a role in CVD.
6. Standardize and prioritize collection of CVD-relevant data at necropsy.

In each case it is clear that there are significant gaps and inconsistencies in what data are currently collected in comparison to what specific and comprehensive information is needed. There is even a lack of consistent terminology and "case definition" criteria among clinicians and pathologists, leading to difficulties in data selection and interpretation for future studies.

RESULTS

In order to achieve the prioritized objectives identified during the planning workshop, the GAHP executive steering committee and project director decided to concentrate first on the creation of a comprehensive CVD database to re-organize the way CVD-relevant clinical and pathology data are collected and used in zoos. This database will be the tool that will facilitate progress toward crucial clinical and research questions to improve ape health and welfare. This database will innovatively adapt a current software model to satisfy this large, cross-disciplinary and cross-taxa need, while building capacity for future generations of zoo professionals. The new database will complement existing record systems by ensuring that CVD-relevant information is centralized and archived and has appropriate layers of confidential access. Creation of the database will have immediate, short-term, and long-term benefits for zoo professionals, and will be a model for future collaborative disease investigations in the broader zoological, conservation, and research communities. In 2012, GAHP leaders applied for an IMLS NLG Demonstration Project to fund the Great Ape Heart Project Database - A Model for Collaborative Disease Investigation.

Because apes are currently affected with CVD and there is a pressing clinical need for an ongoing, centralized system to be able to input and access the available data, coordinate available resources and experienced Subject Matter Experts (SMEs), the project coordinator hired by with the IMLS funding attained in the planning grant, has been given continued funding by Zoo Atlanta. This position will stay as a Zoo Atlanta funded position and the position will report to the project director. The current project manager is on staff at Zoo Atlanta (Marietta Dindo, PhD). Dr. Dindo is currently inputting and archiving all retrospective data, as well as guiding data acquisition prospectively, with the assistance of SMEs. This system is allowing individual zoo veterinarians and their consultants to maximize diagnostic and prognostic tools while the project director and principle investigators, with help from working group participants and executive steering committee members, work on building a more comprehensive database that will be able to define a "best-practice" approach to ape cardiac health. Similarly, the small cadre of specialists who have developed some experience in a

particular ape species, or have invested time across multiple ape species, are currently using this system to access and download information.

Another result of the IMLS-NLG funding has been the establishment of a website dedicated to keeping both participating institutions, interested stakeholders and SME's, as well as the public, informed as the GAHP moves forward. This website can be found at www.thegreatapeheartproject.org and is designed and maintained by the GAHP manager, Dr. Dindo. Maintaining and utilizing ongoing, real-time communication with project stakeholders is the foundation for this projects success.

Another indicator of projected success is the work presently being done by the Project Manager in collecting and organizing gorilla CVD data. Dr. Murphy (GAHP Director) has been collecting cardiac data in a Gorilla Cardiac Database for the last 12 years and working towards compiling some of the CVD-relevant clinical and necropsy data for gorillas. Although the collection of ape CVD data has been historically referred to as a "database" (e.g. Gorilla Cardiac Database, Bonobo Cardiac Database, and the Gorilla Health Project Database), these data are maintained in isolated Excel spreadsheets, with no mechanism for data sharing and comparative analysis.

In 2011, the Project Manager has been able to organize, proof, and archive these data, so that cardiac parameters in individual animals could be assessed by SMEs and reported back to the holding institutions. This process has resulted in a vast improvement in communications and data flow, and news of this groundbreaking project has spread throughout the zoological and research communities. As a result of this interest, there has been an increase in the number of participating institutions and the Project Manager has started receiving CVD-related data collected from orangutans, bonobos and chimpanzees. This preliminary operational test of using a centralized, dedicated resource to facilitate data organization and communications demonstrates that this system will work for zoos, operationally, functionally, and culturally. The test has also demonstrated that gradual accumulation of some data may be possible through the use of volunteers, but the complexity of gathering, analyzing, and reporting ape CVD data requires innovative technology and a focused, adequately-funded effort by a group of highly-trained individuals.

CONCLUSION

The 2011 Planning Workshop resulted in great forward momentum and support from the zoological and research communities. The GAHP Project Coordinator position is funded by the IMLS-NLG and now has matching support from Zoo Atlanta as a Project Manager position. This position has proven to be an active and crucial resource in bridging communication gaps and maintaining the project's momentum. Progress to date on some identified workshop objectives include: the development and use of a standardized cardiovascular examination form for all ape taxa, recruitment of a dedicated Cardiology Advisor for the Orangutan SSP, and recruitment of a dedicated Veterinary Pathologist for the Chimpanzee SSP. In addition, multiple zoos across the USA have started training programs to assess cardiac function in their apes and participation in the GAHP has gained national and international attention. European zoos now have started an offshoot of this project named the European Great Ape Heart Project and we are coordinating efforts at evaluating this disease throughout European ape collections. A

select number of zoos have implanted cardiac monitoring devices in order for us to start some prospective investigations into the development of cardiac disease in apes.

The IMLS-NLG funded February 2011 Workshop established a clear road map of consensus-based action steps needed to achieve exemplary stewardship of captive ape collections. The next logical step in developing a comprehensive database is underway and will connect stakeholders and SMEs; build capacity and communication within and outside of the zoological community; and invest in innovation to solve this issue. The consensus-building workshop process reduced the major risk to this model, which is lack of participation. Specific objectives to achieve the action steps identified through this planning process are:

- ✓ Establish a single cross-disciplinary, accurate database that allows clinicians, pathologists, researchers and other stakeholders to search for CVD-relevant data and carry out appropriate research, diagnostic, and treatment queries;
- ✓ Use expert consultation and coordinated actions to ensure that appropriate, comprehensive and standardized data are collected, acquired, and entered into the database;
- ✓ Expand capacity of current stakeholders, as well as build future partnerships with skilled SMEs and researchers, to elucidate the causes of ape CVD; and
- ✓ Improve communication and dissemination of critical information, within and across scientific and management disciplines.

Zoos across the country play a unique role in preserving and providing access to endangered living collections, and are acutely aware of the toll that CVD takes on the health and welfare of these charismatic animals. As a result, the GAHP consistently garners support from all management levels of AZA. Tangible evidence of this support is the dedicated work of the veterinary and species managers, participation of 52 individuals from 33 institutions at the first IMLS-sponsored workshop, and the increased input of clinical data into the project.

This innovative and forward-thinking effort brought together essential stakeholders from a wide range of disciplines and communities, to develop a timely and coordinated plan to address a critical health need for the great apes. The workshop, white paper, and grant applications resulting from this collaborative planning grant will serve as a national model for investigations addressing health issues in other species, thus improving standards of care in zoological collections.

Appendix 1:

February 2011 Meeting:
We had 52 participants from 33 institutions take part in the GAHP Workshop. Below are summaries of each individual's area of expertise and potential contributions to the project:

Working Group Topics: Communications and record keeping; Pathology; Clinical Group; Etiology of ape CVD

Communications and Record Keeping Working Group
The highest priority goal from this group was the creation of a GAHP comprehensive database and a management system that would sustain the database into the future. Several objectives were identified that would help in the attainment of this goal.

The first step that the group identified as a critical objective was to hire a database manager. This person would then be responsible for managing all cardiac related research activities and job assignments given to SMEs, coordinating access to and information sharing between zoos, research facilities, sanctuaries, and SMEs and providing a point of contact for stakeholders to communicate through. They would also manage a website for disseminating GAHP related forms and information as well as advancing the project's accessibility to the public.

Another critical step was to design a database that would incorporate the critical fields needed to gather as much pertinent data as possible. The data needed to include fields for pathology, clinical and pathological diagnostics, nutrition, treatments, husbandry, research and biomaterials tracking, at a minimum. The database also needed to have the capabilities to link to image-identified fields and a digital histopathological slide scanning dataset in order to maximize and use the data. Each data entry field needs to have standards for data entry developed, and data quality control mechanisms put into place.

Objective number two was to formalize the GAHP data collection process by finalizing the forms that institutions will use when conducting ape health exams, establishing an interim flow of data into the existing database, as well as formalizing a data reporting process so stakeholders and participating institutions have feedback.

Another area of focus identified by this working group was to establish a plan for data access and use, data ownership and confidentiality.

Ensuring consistency and accuracy in data collection was also discussed as an action plan to be built into the design of the database. Tools that could be developed to help ensure data consistency and accuracy were identified as 1) develop a "How to do an echo during an exam" training and reference materials for local cardiologists and echo techs; 2) develop a one-page summary check-list for technicians; 3) establish standard protocols for blood pressure collection, EKGs, etc. during exams; 4) establish standard protocol for gathering necropsy data;

5) standardize guidelines for capturing images; and 6) identify technical experts to troubleshoot image formatting issues.

Another top goal of this committee was to establish species-specific cardiology expert(s) that will commit to developing reference ranges and advising on treatment of ape CVD. This will require coordinated recruitment of cardiologists to interface with veterinary advisors and database manager to establish normal reference ranges for each species to be used throughout the database to delineate “affected” vs. “non-affected” animals.

Communication of the Great Ape Heart Project to wider (zoo and non-zoo) community was also seen as critical to the success of the project. Recruitment of consulting PR/Marketing professionals to aid in developing a PR and Marketing plan for the GAHP, as well as identifying conferences and publications where data generated could be presented to spread the word about the database, were seen as important areas to develop. Communication within the GAHP also needed to be developed and maintained over the length of the project. Establishment of list serves, a website, and active coordination and communication through the project manager, were seen as crucial to these areas. Dissemination and application of results generated by GAHP projects to project participants and researchers, as well as to ape care specialists, was also discussed.

Finally, establishing methods to track current treatments and their effectiveness was seen as a priority that could come out of establishing comprehensive database. Investigating the best ways to track treatment of heart disease in apes, including follow-up for those animals: what medication they're on, when did it start, why was it started, how it was diagnosed, and an annual tracking method were discussed.

Pathology Working Group:

The pathology working group focused on several areas that would strengthen and elucidate links between pathology and clinical data throughout the project. One priority agreed upon was the need to develop and disseminate a standardized clinical data and necropsy form. Currently, gross necropsy and tissue collection is performed by a wide variety of individuals with differing levels of pathology expertise. Adoption and dissemination of a standardized, well-illustrated necropsy protocol will allow all prosectors to collect accurate and comparable data crucial for the pathologic characterization of animals with Great Ape cardiomyopathy.

Another component that this group prioritized as key in elucidating CVD in apes was to identify and implement a third tier of Expertise. A core group of pathologists with the expertise and interest in the identified target organs would develop a lesion identification and scoring system. In order to do this, key pathologists with expertise in renal and cardiac pathology need to be identified and recruited to loom at identified slides within archival collections and a method of digitalization of materials for incorporation / linkage to the GAHP needs to be attained. This would also all aid in development of a standardized histologic evaluation and terminology index.

Another key objective was to have a necropsy reports from each class of great ape reviewed by an SSP pathologist(s) in order to determine prevalence of heart disease in each population and to co-ordinate sample and data submission to the third tier pathologists. After pathologist review, pathology data generated nationally needs to be entered into the GAHP database and /or linked with it via established software, in order to fully characterize the clinicopathologic features of Great Ape cardiomyopathy(s) and gain insight into its pathogenesis (es).
In order to maximize resources at the time of necropsy and to ensure that sample and data collection for the GAHP are not compromised, a prioritized and periodically updated list of biomaterials requests also needs to be established for each species.

Clinical Working Group

The clinical working group also set some defined priorities. The first priority was to define reference ranges for cardiac clinical parameters for each ape species. Identification and recruitment of local resources and species experts for each ape species was seen as a critical first step needed for this goal.
Many of the goals and priorities defined by tis group overlapped with the communications group and are meant to ensure the integrity of data collected and input into the database. Tools that could be developed to ensure this data collection goals were defined as: 1) develop standard data collection template to be used across species; 2) develop a centralized serum bank for future research needs; 3) provide the standard of care information on the ECHO examination and parameters measured for analysis including equipment needs, examination standards, and post-exam analysis templates. Investigations of potential future research opportunities also were discussed as potentials for future development.
Recommendations for “best practices” for anesthetic protocols used for cardiac evaluation procedures were also of interest to investigate.

Another priority goal set by this group was to define which biomarkers are useful in predictive risk assessment, diagnosis and treatment of cardiac disease in ape species, as well as defining the role of cardiac risk factors such as blood pressure, obesity, hyperlipidemia, diabetes mellitus, and renal disease.

A final goal was to develop and disseminate guidelines for cardiac health monitoring, including identification of animals at risk, subclinical disease, clinical disease, and treatment modalities. Definition of life stages for baseline data collection and clinical stages of disease indicating therapy, treatment modalities/drug classes, dosages and indications were seen as a critical next step. Defining dietary therapy recommendations also were discussed.

Etiology Working Group

Several areas of interest were discussed in the etiology working group. The primary focus of discussion was on hypertension**.** Because hypertension is a known cause of hypertrophic cardiomyopathy and myocardial fibrosis in humans, and because the pathological changes in the hearts of great apes are suggestive of those seen in humans with uncontrolled

hypertension, it is imperative that we determine if hypertension is a contributing factor in the fibrosing cardiomyopathy of great apes. Objectives that could help in researching blood pressure and hypertension in apes were identified as: 1) develop a standardized protocol for obtaining awake blood pressure measurements that can be adapted to all ape taxa and develop and distribute a detailed instruction manual to encourage compliance, 2) validate blood pressure measurements in gorillas, 3) investigate other technologies/methods for monitoring BP trends. Comparing in greater detail, the lesions in hearts, kidneys, brains, adrenals from humans with untreated hypertension to sections from similar organs in apes affected with CVD was also discussed.

Another area of possible focus was genetics. In humans, cardiomyopathy (and other types of CVD) often has a genetic component. This association, combined with the high frequency of cardiomyopathy in the captive ape population, suggests that genetics plays a role in the expression of this disease. Recent advances in high throughput sequencing and related reductions in the cost of such genetic analyses have made the identification of mutations associated with cardiomyopathy in apes possible. The use of both molecular genetic techniques and pedigree analysis to determine if there is a genetic component to ape cardiovascular disease was recommended.

Focusing another area of research on obesity and metabolic syndrome was another identified goal. Obesity is a risk factor for CVD in humans and appears to be present in the nonhuman apes. An objective definition of obesity needs to be determined for each ape and whether this is a risk factor for cardiovascular disease. As well as this, a nutritional focus also was a priority. In human and other animals, improper diets can lead to insulin resistance, obesity, and hypertension that can increase the risk of cardiovascular disease. Obesity is not uncommon in captive apes, and there is evidence they have metabolic abnormalities. Differences between the diets of wild and captive apes may contribute to these problems. These dietary differences and the current captive diet need to be examined in relation to risk factors for heart disease.

Another possible etiological area of concern identified was husbandry, exhibit design, and animal personality. Historically, great ape enclosures are limited by size, diversity, and stimulation. In addition, animals may have been managed in unnatural pairings or animal density. This may lead to physical inactivity, boredom, and chronic stress. The goal of this area of examination would be to investigate if there is a link between exhibit design and CVD in great apes.

Investigation of potential concurrent diseases, especially renal disease was also mentioned as an area of interest in this working group. Cardiovascular disease (CVD) is often associated with concurrent diseases in non-ape species, complicating the course of the disease, contributing to its progression, and causing CVD in certain settings. In apes, an association of CVD with kidney, respiratory, and periodontal disease and a role in CVD progression for inflammatory cytokines have been suggested but not yet fully investigated. The goal would be to investigate these links and determine if these concurrent factors play a causal or contributory role in CVD in apes.

Appendix 2: PRIORITIZED WORKSHOP GOALS

Each February 2011 Working Group came up with a list of priorities for the GAHP that were collated at the end of the Workshop. Every participant was given 3 dot stickers in order to vote for his or her top three priorities from the list that was posted. The priorities were then put in descending order based on the number of dots. Some priorities received the same number of dots and therefore share the same priority number.

1. Define reference ranges for cardiac clinical parameters for each ape species (19 dots)
2. Create GAHP database and sustainable management system (16 dots)
3. Determine whether hypertensions is a contributing factor in great ape cardiovascular disease (13 dots)
4. Determine whether diet is related to GAHD (9 dots)
5. Standardize pathology protocols (8 dots)
6. Determine if there is a genetic predisposition for great ape cardiovascular disease (7 dots)
7. Determine which biomarkers are useful in predictive risk assessment, diagnosis and treatment of cardiac disease in ape species. (5 dots)
8. Establish species specific cardiology experts who will commit to developing reference ranges, refining treatment, etc. (3 dots)
8. Disseminate and apply results of GAHP projects (3 dots)
8. Define the role of cardiac risk factors in cardiac disease in ape species (BP, obesity, dyslipidemia, DM, renal disease) (3 dots)
8. Determine whether obesity is related to GAHD (3 dots)
8. ID third tier of expertise (3 dots)
8. Identify funding (3 dots)
14. Communicate the GAHP to the wider zoo and non-zoo community (2 dots)
15. Establish plan for data access and use (1 dot)
15. Formalize GAHP data collection process (flow of data IN) (1 dot)
15. Biomaterials for research (1 dot)
15. Case definition (1 dot)
15. Communication between communities (1 dot)
20. Ensure consistency and accuracy in data collection (0 dots)
20. Formalize process for reporting (flow of data OUT) (0 dots)
20. Ensure treatment protocols are tracked in the database (0 dots)
20. Facilitate communication with GAHP (0 dots)
20. Develop and disseminate guidelines for data collection for at risk, diagnosis, and treatment groups (0 dots)
20. Determine whether exhibit design is related to GAHD, activity levels and obesity (0 dots)
20. Determine whether concurrent diseases contribute to GAHD (0 dots)
20. Examine whether activity levels correlate with obesity (0 dots)
20. Examine whether “personality” is associated with GAHD (0 dots)
20. Pathologist to review every SSP necropsy report (0 dots)
20. National collation of path database (0 dots)
20. Improve communication between clinicians and pathologist (0 dots)
20. Develop mechanism for sharing info between institutions (0 dots)
20. Review mechanism for shipping and storing biomaterials (0 dots)
20. Biomaterials, protection of information (0 dots)
20. Include all relevant systems (renal, respiratory, etc.) (0 dots)
20. Define costs/resources of what is required (0 dots)
20. Digital reference library (0 dots)

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