

**National Animal Genome Research Program (NSRP-8)
2018 Project proposal renewal request**

Reviewer Comments and Response to Reviewers (in blue)

Reviewer number 1

It is very encouraging to perceive the progress of the NRSP-8 program during the last couple of years. As reported in the progress report NRSP-8 seems to have made substantial progress in addressing the stated objectives and goals. NRSP-8 as an umbrella organization appears to have greatly supported the needs of the animal genomics community. The program has made significant improvements in terms of resource scaling, added functionality and engaging researchers from diverse animal genomics communities. Significant developments include efforts in fostering the large community of scientists, development of critical infrastructure to conduct genome-level studies, advance an open-access multi-species bioinformatics tool set, support for sequencing and assembly of genomes, organization of workshops and conferences for effective communication between groups to share results and forge future collaborations, support travel for students and invited speakers, preparation of multi-institutional grant proposals through leveraging NRSP-8 resources to procure additional funding , and formation of large collaborative research groups.

The NRSP-8 has made great strides in adapting new technologies for genome analysis – for example the focus on reference genome sequencing and follow-up population-level genomic studies based on high throughput resequencing technologies; application of the SNP-chip technologies for genomic selection, application of RNA-Seq methods for improved annotations of reference genomes, gene expression studies, development of software tools to integrate available sources of genome and functional data (WGS, SNP, RNA-sequencing, proteomics and metabolomics) in agricultural species to better understand complex phenotypic traits using metabolic syndrome in domesticated animals are a few notable achievements.

The development of the informatics portal (<https://www.animalgenome.org/bioinfo/tools/>) to search, visualize, and share agricultural genomics data is particularly important as it provides a valuable data resource to the community. This site hosts a comprehensive list of all bioinformatics tools and databases developed under the NRSP-8 program and proves to be an extremely useful resource to connect geographically distributed animal genomics communities.

Particularly the initiation of the FAANG consortium in 2014 appears to have accelerated collaborative activities between various animal genomics groups.

The NRSP-8 workshops are an important activity for dissemination of information to stakeholders from the academic, government and industry groups, provides a forum for scientists, students and post docs to share their research and foster future collaborations. The NRSP-8 has effectively used their funding to promote travel for students and post docs to PAG meetings annually. Overall, the reported activities point to promising achievements in the field and fully justify the investments to this program.

Reviewer number 2

Overall:

This proposal is well thought out and on target. While relatively little detail is provided on how many objectives will be achieved, this reviewer finds that level of detail acceptable. I recognize that this document is as much a vision as a recipe for success. Given the success and impact of this group in the past – I am comfortable with most of the details. That being said, there are a few points that could use some more specifics. One concern that I have long held, is that identifying a causative variant is *really* tough... With SNP chips we can identify genomic regions quite readily, but it takes a lot of meiosis to get recombinations within a small region that provide insights that allow one to tease apart the causality of adjacent variants that are in high linkage disequilibrium. There may be new ways to consider this problem using gene editing, for example. This technology is both expensive and unproven in high volume.

Regarding Obj.2.2, we agree with the reviewer. Developing models, algorithms, pipelines to facilitate the identification of causal variants may be hard due to the need for so many meiosis events. However, there is still a need to find more highly predictive variants and/or causal variants when possible. Therefore, the word “causal” was replaced with “causal and/or highly predictive”.

Regarding Obj.2.3, we still think that applying various approaches like CRISPR is needed to characterize the genetic variations previously identified through GWAS as putatively associated with traits. While we acknowledge that these technologies are currently expensive and unproven, there are likely to become more affordable and to be supported by more robust evidence over time.

Some details on how the money from the last proposal was spent would be helpful. There are examples of past coordinator expenses – but these do not provide amounts spent on these items. Similarly, “Research support mini-grants” are listed with few items identifying funding levels.

Examples of past coordinator expenses were provided with the budget request. In addition, the Rewriting Committee invested ample efforts on preparing an accomplishment report that reflects the ROI rather on collecting detailed data on how the money was spent. According to Dr. Eric Yong, the NRSP-8 Accomplishment report was well perceived by the NIFA communications office and by kglobal (ESCAP's communications firm). We will be glad to collect more data on how money was spent, however, given that the budget of each species is handled by a separate experimental station, this will require extra time beyond the current deadline, January 15, 2018.

Addressing the outputs of the two meetings recently held in Beltsville on “Livestock High-Throughput Phenotyping and Big Data Analytics” and “Genome to Phenome: A USDA Blueprint for Animal Production” as they might impact NRSP-8 objectives. Most of the attendees of those meetings were NRSP-8 members.

As the reviewer mentioned below, it is tough to tie this to the G2P workshop in Beltsville before the report is finalized. Therefore, we added a statement that the updated blueprint will be used as a guide.

“Blueprint for USDA Efforts in Agricultural Animal Genomics 2008-2017,” was used as a guide in formulating the objectives for the previous NRSP-8 objectives. While this proposal was due for submission, a new Blueprint document “Genome to Phenome: An USDA Blueprint for Animal Production” was being prepared. The updated blueprint, when available will be used as a guide to adjust the objectives of this proposal”.

Rationale – Grand Challenges:

GC1: How will this challenge be accomplished through funding NRSP-8 differently?

We added this statement “Genomics selection of superior genotypes will help addressing this challenge i.e. enhancing the animal production yields and profitability while reducing the adverse environmental impacts.”

GC2: I challenge the assertion that “Genome-enabled selection practices increasingly account for the effects of genotype on the utilization and assimilation of different animal diets and the potential downstream environmental impacts.” It may be a reasonable goal, but I don’t think we are using genome enabled selection accounting for effects on genotype except for a few large QTL/QTN. I think we are even further away from predicting impacts on downstream impacts. Again, I don’t take issue with this statement as a goal, but I think the statement needs to be adjusted. The GC2 statement calls for development of breeds – I think that could be a laudable objective, particularly in pulling together experiment station resources from multiple states... like was done with NC-1, NC-2, etc.

*We changed the statement to “Genome-enabled selection practices **need to increasingly...**”*

GC3: This seems to be a bit of a reach - I really don’t see where genomics can influence these post-harvest challenges.

To further explain this point we added this statement “Pre- and post- harvesting environments affect shelf-life and quality of the food-animal products. Various genomics approaches allow understanding the biochemical processes through which the animal interacts with the environment pre-, post- and during the harvesting process. In addition, genomics can be used to select for animals that yield products of improved shelf-life and quality and reduced food waste”.

GC5: I am not sure that low-priced is a goal, but rather fair or reasonable priced products. The producer needs to maintain profitability for the enterprise to be sustainable. Certainly, improving efficiencies will help in that effort.

Whanged “low-priced” to “reasonably-priced”.

GC6: A statement about the benefits of animal protein in the diets of people in moderation – especially young children.

We added this statement *“Animal products are excellent source of proteins, fats, vitamins and minerals. Animal proteins contain all the essential amino acids needed for healthy growth especially in children”*.

Objectives:

The sequencing and assembly parts of the objective as written should be accomplished in a year or two – then what? There are several breeds that could use breed specific assemblies (Holstein, Angus, Jersey, Nelore, etc.). It would be interesting to phase the chromosomes of a few important animals from these same breeds. How will the functional annotation be done to accurately ascribe function?

The first specific objective 1.1 was changed to *“Initiate creation of draft genome assemblies for economically important species and breeds for which assemblies are not yet available”*.

Objective 1.2 already mentioned phasing out chromosomes *“Improve existing genome assemblies to close gaps and improve assembly order, especially for highly repetitive sequence regions, such as those in centromeres and on the sex chromosomes”*.

This statement was added to Obj. 1.4 *“The aim is to deliver well-standardized and documented datasets from a set of individuals representing species with reference quality genome assemblies and substantial publicly available phenotypic datasets”*.

It would be nice to tie this to the G2P workshop in Beltsville - I concede that this is tough before the report is finalized... maybe just add a statement that the updated blueprint will be used as a guide.

As in objective 2 -it would make sense to add a statement about using the report from the high-throughput-phenotyping workshop as a guide for prioritizing goals. I think it would make sense for NRSP-8 to provide leadership in warehousing, sharing, and coordinated development of software, scripts, and other software tools.

As mentioned above, page 3 at the end of the introduction to the objectives, this statement was added:

“Blueprint for USDA Efforts in Agricultural Animal Genomics 2008-2017,” was used as a guide in formulating the objectives for the previous NRSP-8 objectives. While this proposal was due for submission, a new Blueprint document “Genome to Phenome: An USDA Blueprint for Animal Production” was being prepared. The updated blueprint, when available will be used as a guide to adjust the objectives of this proposal”.

Reviewer number 3

The NRSP-8 project renewal request demonstrates, in clear and persuasive language, the critical need for support of infrastructure for animal genomics research. The accomplishments for the 2013-2017 period are significant for all species.

As outlined in a recent report sponsored by the National Academy of Sciences¹, among the highest priorities for animal agriculture research investment are optimizing livestock sustainability and productivity. Genomics research is critical for advancing sustainability of animal production. Another application of genomics research not mentioned is the enhancement of nutritional quality and healthfulness of meat products (Strategic Goal 4 of the 2014 USDA Research, Education and Economics Action Plan). It might be worth considering the potential to improve human nutritional outcomes, especially with the public interest in health outcomes linked to meat consumption. For example, genomics has the potential to increase omega-3 levels and other important nutrients, and increase lean meat content, in animal food products.

The is addresses under the contribution of animal genomics to **Grand Challenge 3** from the APLU document:

“Pre- and post- harvesting environments affect shelf-life, nutritional content and quality of food-animal products. Various genomics approaches allow understanding the biochemical processes through which the animal interacts with the environment pre-, post- and during the harvesting process. Genomics research on local breeds and species will allow us to optimize regionally available food systems. Selection of animals best suited for production in a given environment via genomic technologies (precision management systems) can reduce food loss and waste by creating efficient local distribution systems and by selection for animals that produce products with improved shelf-life and quality.”

Under the rationale section, the proposal refers to the “Challenge of Change,²” a document from APLU that is aimed primarily at global food security, which is an interesting choice of reference for the rationale. While much U.S. genomics research is relevant to Challenge of Change, such as understanding climate resilience / tropical adaptation in livestock, disease resistance and potential for zoonotic transmission, one tends to think of U.S. genomics selection as having focused primarily on improved performance of domestic breeds up to now. The question that arises is whether U.S. animal genomics research will shift towards global issues, or continue to focus primarily on U.S. food systems. I respectively suggest the writers consider instead using the One Health concept in the rationale, as this provides a global context for discussing the impact of genomics on food security, antimicrobial resistance, environmental sustainability, animal welfare and human health.

The reviewer is correct that throughout the rationale as presented under the grand challenges and in other places in the document that the concepts of one health are mentioned including food security, environmental impacts, animal health and welfare and impacts on human health. It is unclear how reorganizing these arguments under the umbrella of “one health” will change the outcomes and emphasis

of the NRSP-8. In fact, much of the “one health” community is currently focused on supporting efforts that span two or more components of the animals, humans and the environment triad. Reframing NRSP-8 under the “one health” concept, may unfairly give the impression that the downstream work that NRSP-8 supports is focused across the one health space, whereas NRSP-8 is mainly focused on tools that support research in the “animal” component of the “one health” triad.

Involvement of an industry liaison is a good way to bridge between academia and industry. However, the impact on the animal agriculture industry is not well measured in the accomplishments and impacts section. Is it possible to encourage industry partnership and measure or give examples of the impact on industry? Also, stronger partnerships with NIH and NSF would be highly beneficial to this program.

The committee wonders if the reviewer had a chance to look at the Accomplishment Report that was provided as a separate document in addition to the Accomplishment section in the main document. As example *across species tools developed under objective 2 have allowed the dairy industry used SNP-chips to genotype nearly half a million dairy cattle allowing application of genomic selection which reduced animal selection time (from 5 years to 1 week) and increased genetic merit prediction accuracy by more than 30 percent with an estimated annual benefits of \$100 million per year.*

Several themes consistently emerge in regard to animal genetics and biotechnology research: (1) Social license, (2) Animal welfare, (3) Precision agriculture and (4) Capacity-building.

1. I highly encourage the NSRP-8 coordinators to consider how the program might support outreach and education efforts that would improve the public understanding and perception of animal biotechnologies. Public engagement is critical to preserving the availability of technologies such as gene-editing, and even genomic selection, for future use. As we have seen with GMOs, vaccines and other technologies, lack of transparency and erosion of public trust can have dire consequences for science.

While increasing outreach is a laudable goal, the scope of the NRSP-8 is limited by the budget. Active engagement by industry is sought in this proposal by including industry representatives as part of the technical communities and through species-specific websites and the inclusion of newsletters to update industry as well as other stakeholders for each species and through the bioinformatics coordinator. Without increasing the total budget allotment for NRSP-8 it was unclear to the writing committee how we could dramatically increase the amount of resources invested in outreach that would address the broad goals encompassed by NRSP-8.

2. Genetic selection has resulted in dramatic improvements in livestock performance in the last 50-100 years. For some species, these gains are still needed, yet for others it is time to shift to addressing challenges to health and wellbeing, and the environment.

Use of genetic technologies to advance the health and well-being and environmental impacts of animal agriculture is encompassed broadly throughout the document and references to “phenotype and important phenotypes” would include phenotypes that are relevant to health, well-being and the environment. As mentioned in the proposal, “While applying genetic tools to improve production and resilience of animals, we must account for animal health and welfare”

3. A topic of high interest at meetings including the Genome to Phenome 2017 meeting is the development of precision tools including rapid diagnostics, precision monitoring, digital- or cloud-based programs for animal management and others. High-throughput phenotyping tools, to make associations between genotype and phenotype, are needed.

These tools are addressed under Objective 2.4, to clarify we have added the phrases in red: *“Support deep phenotyping of important traits at the molecular, cellular, tissue and organismal levels, including the use of high-throughput technologies such as transcriptome sequencing, proteomics and metabolomics studies, whole-animal parameter monitoring, in vitro gene mutagenesis screening analyses and other tools to support precision monitoring.”*

4. There is a major need for agricultural scientists skilled in bioinformatics, data analytics, computer sciences, etc. I highly encourage the NRSP-8 program to support training opportunities in these fields for their students, in addition to the annual Plant and Animal Genome meeting.

Given the limited funds available for NRSP-8, we recommend using short-term face-to-face courses and online classes. The following objectives were modified to capture reviewer’s recommendation.

Obj. 1.9. Train the next generation of animal breeders in applying and developing new data analytics methods based on high-throughput genomic data to make genetic progress through online and face-to-face short courses.

Obj. 3.4. Help in training students/postdocs to be future leaders in agriculture-oriented bioinformatics, data and computational sciences.

Additional recommendations:

- High-density SNP chips that work across breeds, especially in the beef industry, that would allow selection for traits such as heat tolerance or disease resistance

This is directly supported under objectives 2.1.

- Identification of SNPs/QTLs that facilitate antimicrobial stewardship (e.g. resistance to BRD in cattle or coccidiosis in poultry, which often lead to antibiotic treatment for secondary infections).

This is directly supported under objectives 2.8.

- Better understanding of the role of regulatory elements and non-coding DNA in determining phenotype.

This is supported under objectives 1.4 and 1.5 as well as 2.2 and 2.5

- Infrastructure support for metagenomic/microbiome research to better understand gut health, reference populations linked with animal genome, microbial dynamics and selection pressure, and animal health and welfare under antibiotic-free production practices

This is addressed and directly supported under Objective 2.8: *“Advance metagenomic studies to help in discovery of novel pathogens, understanding host-pathogen interaction and determining the role of microbiota in agri-animal nutrition, health and reproductive performance.”*

REFERENCES

¹Committee on Considerations for the Future of Animal Science Research; Science and Technology for Sustainability Program; Policy and Global Affairs; Board on Agriculture and Natural Resources; Division on Earth and Life Sciences; National Research Council. Critical Role of Animal Science Research in Food Security and Sustainability. Washington (DC): [National Academies Press \(US\)](#); 2015 Mar 31. Summary available from: <https://www.ncbi.nlm.nih.gov/books/NBK285709/>

²<http://www.aplu.org/projects-and-initiatives/international-programs/challenge-of-change/index.html>