Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is "None", please specify "None" as your response. "Not applicable" is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format. Questions? Contact Health Research Program staff at 717-231-2825.

1. **Grantee Institution:** The Pennsylvania State University

2. **Reporting Period (start and end date of grant award period):** 1/1/2011 - 12/31/2014

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** John Anthony, MPA

4. **Grant Contact Person's Telephone Number:** 814 935 1081

5. **Grant SAP Number:** 4100054865

6. **Project Number and Title of Research Project:** 9. *Genomics of Amyotrophic Lateral Sclerosis*

7. **Start and End Date of Research Project:** 5/29/2013 – 12/31/2014

8. **Name of Principal Investigator for the Research Project:** Zachary Simmons, MD

9. **Research Project Expenses**.

   9(A) Please provide the total amount of health research grant funds spent on this project for the entire duration of the grant, including indirect costs and any interest earned that was spent:

   $ 539,240

   9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project	Cost
Reed, Cynthia	Human Research Tech	42%	$16,500 sal
Bowman, James	Research Tech	47%	$16,500 sal
Zachary Simmons	PI	Average 3%	$8,984 sal

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project
Simmons	Principal Investigator	20
Broach	Professor, Co-PI	10
Gerhard	Professor, Co-PI	10
Sheldon	Manager, IPM	10
Schneper	Assist Prof., Bioinformatician	20
Nguyen	Graduate Student	30
Russo	Graduate Student	10

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

Type of Scientific Equipment	Value Derived	Cost
Partial match of Ion Proton System	Provides a more rapid turnaround for targeted sequencing experiments	$119,315
Partial match of ISCAN system	Provides for extremely high density genotyping of human DNA	$54,022

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes_____ No__X___

If yes, please indicate the source and amount of other funds:

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes___X___ No_____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert "not funded" in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds awarded:
Genomic analysis of sporadic ALS	☐NIH ☐ Other federal (specify:_____) X Nonfederal source (specify: ALS Assn)	1/2015	$240,000	$ Application currently under review

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes___X____ No_____

If yes, please describe your plans:

We will be soliciting support from private individuals as well as philanthropic organizations, such as ALS Association. We also plan to apply to NIH for funding to evaluate the role of genes identified in this study in ALS by studies in model organisms such as zebrafish and mice.

12. Future of Research Project. What are the future plans for this research project?

a. We will continue to sequence the genomes of sporadic ALS patients, particularly those for whom we can also consent both parents;
b. We will develop computational methods for determining chromosome phasing in order to identify those patients carrying compound heterozygous mutations in genes likely relevant to the disease in those patients for which we do not have sequence information from the parents;

c. We will explore the relevance of possible new ALS genes identified in this study by eliminating the gene in model organisms – zebrafish and mice – and examining the phenotype of the resulting deletion mutants.

13. **New Investigator Training and Development**. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes___X___ No_____

If yes, how many students? Please specify in the tables below:

	Undergraduate	Masters	Pre-doc	Post-doc
Male			1	
Female			1	
Unknown				
Total			**2**	

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic			1	
Non-Hispanic			1	
Unknown				
Total			**2**	

	Undergraduate	Masters	Pre-doc	Post-doc
White				
Black				
Asian			1	
Other			1	
Unknown				
Total			**2**	

14. **Recruitment of Out-of–State Researchers**. Did you bring researchers into Pennsylvania to carry out this research project?

Yes_____ No___X_____

If yes, please list the name and degree of each researcher and his/her previous affiliation:

15. **Impact on Research Capacity and Quality**. Did the health research project enhance the quality and/or capacity of research at your institution?

Yes___X____ No_____

If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

We installed and extensively developed genomic software packages for analysis of exome and whole genome sequencing. In addition, we purchased an Illumina iSCAN array scanner for bead based genotyping of genomic material. This new instrument provides for extremely high density genotyping of human DNA as well as that from a variety of organisms and vastly expands the capabilities of the Penn State Institute for Personalized Medicine's (IPM's) Genomics Core. Finally, we purchased a Life Technologies Ion Proton DNA sequencing instrument to complement the Illumina sequencers currently in the Genomics Core. The instrument permits a more rapid turnaround for targeted sequencing experiments than does the Illumina instruments and provides a second sequencing technology to improve the accuracy of the genome and exome sequencing. In sum, these instruments provide Penn State investigators with all the genomics tools currently viewed as state-of-the-art. As a consequence, investigators are not limited technologically in competing in the genomics arena.

16. Collaboration, business and community involvement.

16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

Yes___X____ No_____

If yes, please describe the collaborations:

We have established a collaboration with Brian Traynor at the NIH to participate in an extensive Genome Wide Association Study to identify new genes contributing to ALS. We are also in discussion regarding collaboration with investigators at the New York Genome Center and Columbia.

16(B) Did the research project result in commercial development of any research products?

Yes_____ No___X_____

If yes, please describe commercial development activities that resulted from the research project:

16(C) Did the research lead to new involvement with the community?

Yes___X__ No_____

If yes, please describe involvement with community groups that resulted from the research project:

The IPM has reached out to the community in a variety of town hall meetings over the last two years to explain the value of genomic research and to encourage members of the community to participate. We have also worked with ALS World Wide to address the ALS community with regard to participating in research projects.

17. Progress in Achieving Research Goals, Objectives and Aims.

List the project goals, objectives and specific aims (as contained in the grant agreement). Summarize the progress made in achieving these goals, objectives and aims for the period that the project was funded (i.e., from project start date through end date). Indicate whether or not each goal/objective/aim was achieved; if something was not achieved, note the reasons why. Describe the methods used. If changes were made to the research goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. Provide detailed results of the project. Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations at the end of the summary of progress; peer-reviewed publications should be listed under item 20.

This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still include enough detail for the expert peer reviewers to evaluate the progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project work using this Final Progress Report, all project Annual Reports and the project's strategic plan. After the final performance review of each project is complete, approximately 12-16 months after the end of the grant, this Final Progress Report, as well as the Final Performance Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (ß) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

Amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease, is a devastating neurological disease for which there is no effective therapy. Approximately 5-10% of cases are inherited, while a genetic basis for the remaining cases has not yet been determined. The primary objective of this project is to further define the genetic architecture of ALS. Our goal is identify new mutations and new genes associated with ALS. *Our specific aims are to 1) Establish processes for consenting ALS patients and collecting biological samples (e.g., saliva, blood, etc.) for sequence analysis; 2) Conduct targeted sequence analysis of known familial ALS (FALS) genes in patients recruited in aim 1; 3) Conduct whole genome/exome sequencing on selected patients who do not have mutations in known FALS genes.* The Penn State Institute for Personalized Medicine (IPM) will facilitate recruiting strategies and will work closely with the ALS clinic in consenting participants, data capture, and sample acquisition. DNA will be isolated from biological samples and subject to next generation sequencing in the IPM Genomics Core facility. Analysis of DNA sequence data will be performed in the Bioinformatics core of the IPM. The discovery of new mutations in known genes will be analyzed in the context of detailed phenotype data collected by the PI and his clinic staff to identify possible clinical heterogeneity. New genes identified will be targets for future drug discovery efforts.

The primary focus of this research project is to identify the genetic underpinnings of amyotrophic lateral sclerosis (ALS), particularly in those patients who present with no family history of the disease. The work is conducted as a collaborative effort between the ALS clinic within the Penn State Hershey Neuroscience Institute ("Clinic") and the Institute for Personalized Medicine ("IPM"). Results from this study should yield insights into the diverse mechanistic bases of the disease and thereby pinpoint the therapeutic approaches that might prove efficacious and identify which patients might respond to which treatment.

To achieve this end, we proposed three specific aims to be completed under support of this grant and have made significant progress in all aims:

Aim 1. Establish processes for consenting ALS patients and collecting biological samples (e.g., saliva, blood, etc.) for sequence analysis.

We have established a seamless process for consenting patients and collecting samples. We have embedded consenters in the Clinic to meet with and consent patients under an approved IRB protocol. We then either add a request for an extra blood sample to be drawn in the course of their normal clinical blood work or provide patients or other family members with saliva kits to collect saliva samples. Our consent rate in the clinic has been remarkably high, with greater that 95% of patients agreeing to participate in this study. As of December 31, 2014 we had consented 293 patients and 79 family members including 30 parents comprising 12 complete trios (ALS patient plus both parents). We have obtained blood or saliva samples, both suitable for DNA sequence analysis, from 233 patients and 79 family members.

Aim 2. Conduct targeted sequence analysis of known familial ALS (fALS) genes in patients recruited in aim 1.

The number of genes identified as causative of familial ALS has recently grown to >20 for those rigorously associated by linkage analysis and >100 suspected to be associated by indirect methods. Consequently, the cost of specifically sequencing the known genes in a patient's genomic DNA sample is greater than the cost of sequencing the entire exome. Accordingly, we

have eschewed this approach to studying ALS genetics in our cohort and have rather gone directly to exome sequencing for all patients. Thus, this aim has been subsumed into Aim 3.

Aim 3. Conduct whole genome/exome sequencing on selected patients who do not have mutations in known FALS genes.

Previous observations have established that only 5-10% of ALS patients have a family history of the disease, which means that >90% of patients have no near relatives who have presented with the disease. However, twin studies have estimated that ALS heritability to be 60-70%, suggesting that many patients who present with sporadic ALS (sALS) may have an underlying genetic cause. Accordingly, we have focused on patients with apparently sporadic forms of the disease to determine whether unidentified genetic factors are contributing to the disease.

<u>fALS</u>. We have sequenced the exomes of eight fALS patients and are in the process of exploring whether these patients carry known causative variants in known ALS genes. This is the case for three patients: one carries the previously identified D91A in SOD1, one carries the previously described N87S variant in SOD1 and one patient carries the previously identified G223G224Δ in FUS. In addition, one patient carries a likely deleterious variant in ARHGEF28, a suspected ALS causative gene. This analysis is still ongoing.

<u>c9ORF72</u>. A recent report suggested that a hexanucleotide repeat expansion in the c9ORF72 gene was associated with a significant number of fALS and sALS patients. Accordingly, we developed an assay to determine the repeat length of this repeat element and then applied that assay to a number of our ALS patients' genomes. We have found 2 examples of repeat expansion in 137 genomes examined, significantly lower than the 33% of repeat expansions in fALS patients and 10% of repeat expansions of sALS patients previously reported.

The pathological effects of C9orf72 repeats are evident at repeat lengths of greater than 30. Those variants with shorter repeat length have not been considered deleterious. However, in a separate study examining certain cognitive functions of ALS functions, we have identified a strong correlation between repeat length in the 5-30 repeat range and the cognitive level of the patients. That is, the longer the repeat length, the lower the cognitive score. This is a remarkable finding since it suggests that the C9orf72 locus affects intellectual activity at repeat lengths that had previously been determined to be benign. We are exploring this observation in more detail.

<u>sALS trios</u>. An effective mechanism for identifying mutations that might contribute to the onset of disease in patients who have no family history of the disease is to compare the sequence of the genome of the affected patient to that of their parents. This analysis identifies mutations that might have arisen de novo in the patient and which might affect a gene in a way that leads to ALS. This analysis also identifies genes in which the patient inherited different defective alleles from each of his parents but for which each parent was heterozygous and thus carried one normal version of the gene. We would assume that in this case the loss of function of the gene in question would be deleterious but loss of only one of the alleles in an individual would not be deleterious. Such a situation, referred to as compound heterozygosity, would appear to be a case of sporadic ALS, since neither family would exhibit a history of ALS, since all family members would likely carry at least one normal copy of the gene. To accomplish this goal, we have collected samples from ten patients and both of their parents and completed exome sequencing of all thirty individuals. In addition, we have conducted genotype array analysis on all trio samples.

These data are useful for confirming sequencing results and, more importantly, for identifying copy number variants CNV that might contribute to disease onset or progression. One such example is noted below.

Trio 1. We identified no *de novo* mutations in this patient but we did identify compound heterozygous variants in two genes, whose known functions suggest a possible involvement in ALS. One gene, DYNC2LI1, encodes the light chain of dynein type 2. Mutations of dynein have been shown to produce motor disorders similar to ALS. Moreover, the product of DYNC2LI1 has been shown to interact with SOD1, the product of gene mutations which are linked to fALS. The second gene, COL6A1, encodes collagen VI. Mutations in this gene have been associated with myopathy disorders. In addition, we identified in the patient a de novo 3 Mb deletion in one homolog of chromosome 11, which spans at least thirteen genes, potentially rendering one or more of them haplo-insufficient. One of those genes encodes a heat shock protein that associates with mutant SOD1 in the spinal cord of transgenic mice. We confirmed this deletion by Sanger sequencing and identified the precise breakpoint. This patient has since deceased and an analysis of her medical record indicates that her disease progressed rapidly, with death occurring only fourteen months after the onset of symptoms. We surmise that this rapid progression may have resulted from the cumulative effect of the multiple causative genetic variants present in her genome.

Trio 2. We identified compound heterozygosity in two genes in this patient, NRP2 and RP1L1. NRP2 encodes neuropilin 2, which may play a role in cardiovascular development, axon guidance and tumorigenesis. RP1L1 is involved in retinitis pigmentosa and encodes a protein that binds to microtubules. However, its expression is limited to the retinal neurons, which are not affected in most cases of ALS.

Trio 3. We identified compound heterozygosity in two genes in this patient, MYO7A and B4GALNT3. MYO7A encodes myosin 7, mutations of which have been linked to myodystrophies. B4GALNT3 encodes an enzyme that transfers N-acetylgalactosamine onto glucosyl residues to form N,N'-diacetyllactosediamine (terminal structure of cell surface N-glycans).

Trio 4. We identified compound heterozygosity in one gene in this patient, STARD9, which encodes a microtubule-dependent motor protein required for spindle pole assembly during mitosis. While neuronal cells are not generally undergoing mitosis, the gene is expressed extensively in the brain, particularly the cerebellum. This suggests that STARD9 may have microtubule associated functions in addition to those in mitosis and thus is a reasonable candidate for an ALS related gene.

Trio 5. We identified compound heterozygosity in three genes in this patient, KIDINS220, KNTC1, and PCDHB9, as well as a potentially inactivating variant in the X-linked DMD gene. KIDINS220 has been linked to Alzheimer's disease and DMD to myodystrophies. KNTC1 is involved in promoting dynein/dynactin functions and PCDHB9 encodes a calcium dependent cell adhesion protein. Any of these genes could be required for neuronal survival.

Trio 6. We identified compound heterozygosity in one gene in this patient, MYO3A, which encodes an unusual myosin. However, expression of this gene is restricted to the cochlea and the retina and has only been associated with hearing loss.

Trio 7. We identified compound heterozygosity in several genes in this patient as well as a number of rare, likely debilitating variants, in several X-linked genes. We will continue exploring the potential role of these genes in ALS.

Discordant Monozygotic Twins. Two of the patients on whom we have performed exome sequence analysis each has a monozygotic twin who has not exhibited any symptoms of ALS. Accordingly, we have examined the sequences of both pairs of twins to assess whether the limited genetic difference between the two twins might point to a causative gene in the affected twin or a protective variant in the unaffected twin. In one pair, the affect twin carries a deletion in one copy of *FGGY* that is not present in the unaffected twin. FGGY encodes a protein that phosphorylates carbohydrates such as ribulose, ribitol, and L-arabinitol. Genome-wide association studies in some populations have found an association between polymorphisms in this gene and sporadic amyotrophic lateral sclerosis, but studies of other populations have not been able to replicate this association. We are still analyzing data from twin set 2.

Future Research Outcomes and Benefits

This project has developed tools to identify mutations in both known genes and new genes related to Amyotrophic Lateral Sclerosis (ALS), or Lou Gehrig's disease, a neurodegenerative disease characterized by progressive degeneration of motor neurons of the brain, brainstem, and spinal cord. The project has also pinpointed a number of candidate genes whose role in ALS is likely causative. The identification of known mutations will allow for fine-grained analysis of the clinical spectrum of ALS in relation to specific mutations in order to determine whether subclinical heterogeneity exists. The identification of new genes will enable studies into disease mechanism and may provide new insight into the pathogenesis of ALS. New genes will also serve as targets for the development of pharmaceuticals, permitting targeting of subtypes of ALS based on genetics and pathogenesis, in place of the current crude therapeutic trials, which are aimed broadly at the ALS phenotype, and have generally been unsuccessful. To date, there is only one FDA-approved drug for ALS (riluzole) which extends lifespan, on average, 60-90 days. Our results and developed methodology should expand the feasibility of targeted therapeutic development to generate treatments that are truly effective.

18. Extent of Clinical Activities Initiated and Completed. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be "No."

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
__X__No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

____Yes
__X_No

If "Yes" to either 18(A) or 18(B), items 18(C) – (F) must also be completed. (Do NOT complete 18(C-F) if 18(A) and 18(B) are both "No.")

18(C) How many hospital and health care professionals were involved in the research project?

_____Number of hospital and health care professionals involved in the research project

18(D) How many subjects were included in the study compared to targeted goals?

_____Number of subjects originally targeted to be included in the study
_____Number of subjects enrolled in the study

Note: Studies that fall dramatically short on recruitment are encouraged to provide the details of their recruitment efforts in Item 17, Progress in Achieving Research Goals, Objectives and Aims. For example, the number of eligible subjects approached, the number that refused to participate and the reasons for refusal. Without this information it is difficult to discern whether eligibility criteria were too restrictive or the study simply did not appeal to subjects.

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

Gender:
_____Males
_____Females
_____Unknown

Ethnicity:
_____Latinos or Hispanics
_____Not Latinos or Hispanics
_____Unknown

Race:
_____American Indian or Alaska Native
_____Asian
_____Blacks or African American
_____Native Hawaiian or Other Pacific Islander
_____White
_____Other, specify:_____
_____Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was conducted.)

19. Human Embryonic Stem Cell Research. Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?
_____Yes
___X_ No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?
_____Yes
_____ No

19(C) Please describe how this project involved human embryonic stem cells:

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication or paper submitted for publication, listed in the table, in a PDF version 5.0.5 (or greater) format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, and an abbreviated title of the publication. For example, if you submit two publications for Smith (PI for Project 01), one publication for Zhang (PI for Project 03), and one publication for Bates (PI for Project 04), the filenames would be:

Project 01 – Smith – Three cases of isolated
Project 01 – Smith – Investigation of NEB1 deletions
Project 03 – Zhang – Molecular profiling of aromatase
Project 04 – Bates – Neonatal intensive care

If the publication is not available electronically, provide 5 paper copies of the publication.

Note: The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1. None				☐Submitted ☐Accepted ☐Published

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes____X____ No_____

If yes, please describe your plans:

We are currently writing three manuscripts based on the work supported by the CURE funding. The first is a case study of the patient described in Trio 1 above. The second is a compilation of the data acquired to date on the exome sequence of the 100 or so patients we have sequenced, with an emphasis on the prevalence of rare compound heterozygotes in genes potentially causative of the disease. The third describes the effect of c9orf72 repeat length on cognitive function.

21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project. Describe the outcome, impact, and effectiveness of the research project by summarizing its impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

We are still in the process of analyzing and correlating our genome sequence data with the details of ALS disease progression. However, we have already obtained indication that the particular genetic alteration responsible for the disease may also influence the progression of the disease. For instance, both the SOD1 D90A and N87S mutations identified in two of our patients with familial ALS are associated with indolent forms of the disease. On the other hand, the patient of trio 1 carried multiple mutations potentially contributory to the disease and experienced a very rapid disease progression. Accordingly, early identification of the underlying genetic basis of the disease in ALS patients may well offer the clinician an indication of the likely trajectory of the disease and thereby help prepare the patient for their subsequent experience.

22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment. Describe major discoveries, new drugs, and new approaches for prevention, diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert "None"; do not use "Not applicable."

Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

None

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes_____ No___X_____

If "Yes" to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is "No.")

a. Title of Invention:

b. Name of Inventor(s):

c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):

d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No___

If yes, indicate date patent was filed:

e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No___
If yes, indicate number of patent, title and date issued:
Patent number:
Title of patent:
Date issued:

f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes_____ No___

If yes, how many licenses were granted?_____

g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes__ No___

If yes, describe the commercial development activities:

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes_____ No___X_____

If yes, please describe your plans:

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Simmons, Zachary	Professor of Neurology and Humanities
eRA COMMONS USER NAME (credential, e.g., agency login) Zsimmons	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Dartmouth College, Hanover, NH	BA	06/78	Biochemistry
University of Florida, Gainesville, FL	MD	05/82	Medicine

A. Personal Statement

The goals of the research are 1) Establish processes for consenting ALS patients and collecting biological samples (e.g., saliva, blood, etc.) for sequence analysis; 2) Conduct targeted sequence analysis of known familial ALS (FALS) genes in patients recruited in aim 1; 3) Conduct whole genome/exome sequencing on selected patients who do not have mutations in known FALS genes. As a clinician and clinical researcher, I have a longstanding interest in ALS, having participated or collaborated in both clinical and basic science research. Our ALS center is a regional, multidisciplinary clinical and research center. In my role as director of our institution's ALS Center and Neuromuscular Program, I care for all these patients personally, and am responsible for recruitment of our patients into clinical research, for supervising 3 research coordinators, and for coordinating all communication and collaboration between our clinical enterprise and various research studies. My role on the project, PI, was to identify those patients at our center with ALS, to recruit them into this study if they are interested and willing, and to collaborate with basic science colleagues in creating a database of clinical and genetic data which could be used to achieve the goals of the research.

B. Positions and Honors

Positions and Employment

1982 - 1983	Resident in Medicine, University of Iowa, Iowa City, IA
1983 - 1986	Resident in Neurology, University of Iowa, Iowa City, IA
1990 - 1992	Fellow in EMG and Neuromuscular Diseases, University of Michigan, Ann Arbor, MI
1992 - 1997	Assistant Professor, Division of Neurology, Penn State College of Medicine
1992 -	Director, Clinical Neurophysiology Lab and Neuromuscular Program, Penn State Milton S. Hershey Medical Center, Hershey, PA
1993 -	Director, MDA Clinic, Penn State Milton S. Hershey Medical Center, Hershey, PA
1995 -	Director, ALS Center, Penn State Milton S. Hershey Medical Center, Hershey, PA
1997 - 2002	Associate Professor, Division of Neurology, Penn State College of Medicine

2002 -	Professor, Department of Neurology (formerly Division of Neurology), Penn State College of Medicine
2009 -	Research Professor, Department of Psychology, Philadelphia College of Osteopathic Medicine, Philadelphia, PA
2011-	Professor, Department of Humanities, Penn State College of Medicine

Other Experience and Professional Memberships

1989 -	Member, American Academy of Neurology (currently a fellow)
1989 -	Fellow, American Association of Electrodiagnostic Medicine
1997 -	Member, Graduate School Faculty, Penn State University, State College, PA
1998 - 2006	Member, Program Committee, American Association of Electrodiagnostic Medicine
2000 - 2004	Member and chair, Maintenance of Certification Committee, ABEM
2001 -	Member, American Neurological Association
2004 -2012	Member and chair, Exam Committee, American Board of Electrodiagnostic Medicine
2004 -	Member, Promotion and Tenure Committee, Penn State Department of Neurology
2006 -	Member, Ethics Committee, Penn State Hershey Medical Center
2012 -	Member, Board of Directors, American Association of Neuromuscular and Electrodiagnostic Medicine
2012 –	Senior Associate Editor, *Muscle & Nerve*

Honors

1978	Phi Beta Kappa, Dartmouth College
1981	Alpha Omega Alpha, University of Florida College of Medicine

C. Selected Peer-reviewed Publications (Selected from 95 peer-reviewed publications)

Most relevant to the current application

1. Simmons Z, Felgoise SH, Bremer BA, Walsh SM, Hufford DJ, Bromberg MB, David W, Forshew DA, Heiman-Patterson TD, Lai EC, McCluskey L. The ALSSQOL: balancing physical and non-physical factors in assessing quality of life in ALS. *Neurology*. 2006;67:1659-1664.
2. Flaherty-Craig C, Brothers A, Dearman B, Eslinger P, Simmons Z. Penn State screen exam for the detection of frontal and temporal dysfunction syndromes: application to ALS. *Amyotroph Lateral Scler*. 2009;10:107-112.
3. Mitchell RM, Freeman WM, Randazzo WT, Stephens HE, Beard JL, Simmons Z, Connor JR. A CSF biomarker panel for identification of patients with amyotrophic lateral sclerosis. Neurology 2009;72:14-19.
4. Murphy V, Felgoise SH, Walsh SM, Simmons Z. Problem-solving skills predict quality of life and psychological morbidity in ALS caregivers. *Amyotroph Lateral Scler* .2009;10:147-153.
5. Felgoise SH, Stewart JL, Bremer BA, Walsh SM, Bromberg MB, Simmons Z. The SEIQoL-DW for assessing quality of life in ALS: strengths and limitations. *Amyotroph Lateral Scler*. 2009;10:456-462.
6. Mitchell RM, Simmons Z, Beard JL, Stephens HE, Connor J. Plasma biomarkers associated with ALS and their relationship to iron homeostasis. Muscle Nerve 2010;42:95-103.
7. Felgoise SH, Chakraborty BH, Bond E, Rodriguez J, Bremer BA, Walsh SM, Lai EC, McCluskey L, Simmons, S. Psychological morbidity in ALS: the importance of psychological assessment beyond depression alone. *Amyotroph Lateral Scler*. 2010;11:351-358.

8. Cupp J, Simmons Z, Berg A, Felgoise SH, Walsh SM, Stephens HE. Psychological health in patients with ALS is maintained as physical function declines. Amyotroph Lateral Scler 2011;12:290-296.
9. Zamietra K, Lehman EB, Felgoise SH, Walsh SM, Stephens HE, Simmons, Z. Noninvasive ventilation and gastrostomy may not impact overall quality of life in patients with ALS. Amyotroph Lateral Scler 2012;13:55-58.
10. Su XW, Lee SY, Mitchell RM, Stephens HE, Simmons Z, Connor JR. H63D HFE polymorphisms are associated with increased disease duration and decreased muscle SOD1 expression in amyotrophic lateral sclerosis patients. Muscle Nerve 2013;48:242-246.
11. Su XW, Simmons Z, Mitchell RM, Kong L, Stephens HE, Connor JR. Biomarker-based predictive models for prognosis in amyotrophic lateral sclerosis. JAMA Neurology 2013;70(12):1505-1511.
12. Su XW, Clardy SL, Stephens HE, Simmons Z, Connor JR. Serum ferritin is elevated in amyotrophic lateral sclerosis patients. Amyotroph Lateral Scler Frontotemporal Degener (Accepted article, doi 10.3109/21678421.2014.984723)

Additional recent publications of importance to the field (in chronological order)

1. Flaherty-Craig C, Eslinger P, Stephens B, Simmons Z. A rapid screening battery to identify frontal dysfunction in patients with ALS. *Neurology*. 2006;67:2070-2072.
2. Hossler C, Levi BH, Simmons Z, Green MJ. Advance care planning for patients with ALS: feasibility of an interactive computer program. *Amyotroph Lateral Scler.* 2011;12:172-177.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
James R. Broach	Distinguished Professor and Chair
eRA COMMONS USER NAME jbroach	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Yale University	B.S.	1969	Chemistry
Univ. of California	Ph.D	1973	Biochemistry
Univ. of California	Post Doc	1974-1976	Medical Physics
Cold Spring Harbor Laboratory	Post Doc	1976-1977	Genetics

A. Personal Statement

I have directed successful genetics and genomic research programs for more than thirty five years, both in academic settings at SUNY Stony Brook and Princeton and in the biotechnology industry at Cadus Pharmaceuticals. During much of that time I pursued research in molecular biology of the yeast *Saccharomyces* during which I developed a number of technologies in the field – including the first application of chromatin immunoprecipitation in yeast - and promoted the use of yeast as a model system, in part through editing a number of volumes on the *Molecular Biology of the Yeast Saccharomyces*. I have spent the last decade promoting genomics and systems biology as coDirector of one of the first NIH Centers of Excellence in Computational Biology and as the first Director of the of the Lewis Sigler Institute for Integrative Genomics, where we brought together investigators in physics, computer sciences, chemistry, chemical engineering and biology under one roof to develop tools to integrate large data sets from genome-wide biological experiments and extract general principles from that integration. I also promoted the development of systems biology as the first chair of Genomics, Computational Biology and Technology NIH Study Section.

More recently, I have redirected my interest in the genomics of model systems to the application of genomic tools to issues of disease onset and treatment, through my position as the inaugural Director of the Penn State Hershey Institute for Personalized Medicine. The Institute comprises a biorepository, in which biological samples from all consented patients of the Hershey Medical Center are being stored; a genomics core, in which state of the art genotyping and NextGen sequencing is applied to the biological samples; and a bioinformatics core, in which patient outcome data obtained from electronic medical records are correlated with genomic profiling and sequencing results. I work closely with clinicians at Hershey Medical Center to identify patients who are members of families in which the disorder or response to treatment shows a familial pattern of inheritance as well as cohorts of patients that have phenotypically distinct disease presentations or responses to treatment. We have successfully inaugurated studies in ALS, Parkinson's, IBD, MS and osteoporosis. Finally, we work closely with Department of Public Health Sciences to explore the environmental, ethical and economic consequences of implementation of personalized medicine.

B. Positions and Honors

1977 - 1979	Cold Spring Harbor Laboratory, Staff Scientist
1979 - 1984	State University of New York at Stony Brook, Assistant/Associate Professor
1984 - 2012	Princeton University, Professor
1992 – 1999	Director of Research, Cadus Pharmaceuticals Inc.
2001 – 2008	Associate Director, Lewis-Sigler Institute of Integrative Genomics
2004 - 2012	Associate Chair, Dept. of Molecular Biology, Princeton University
2012 – present	Professor Emeritus, Princeton University
2012 – present	Professor and Chair, Dept. of Biochemistry and Molecular Biology, Penn State University College of Medicine
2012 – present	Director, Penn State Hershey Institute for Personalized Medicine

1974 - 1975	American Cancer Society Postdoctoral Fellow
1983 - 1987	American Heart Association Established Investigator
1983 - 1987	Member, NIH Genetics Study Section
1984 - 1988	Associate Editor, Molecular and Cellular Biology
1984 - 1991	Associate Editor, Cell
1988 - 1993	Frederick Cancer Center, Scientific Review Board
1993	Chairman, Gordon Conference on Plasmid and Chromosome Dynamics
1994 - present	Fellow, American Academy of Microbiology
1991 - 2000	Editor, *Molecular and Cellular Biology*
1986 - present	Life Sciences Research Foundation, Co Director and Review Board Member
1995 – present	Director, Molecular Basis of Cancer Training Program
2002 – 2004	Member, NIH Genomics Study Section
2004 – 2006	Chair, NIH Genomics, Computational Biology and Technology Study Section
2004 – 2012	Associate Director, NIH Center of Excellence in Computational Biology
2004 – 2012	Commissioner, New Jersey Commission on Cancer Research
2005 – 2013	Member, Organizing Committee, GSA Yeast Meetings
2005 – present	Executive Committee, President (2011) and Treasurer (2013-2015), Cancer Biology Training Consortium
2007 – 2012	Member, Board of Trustees, University of Medicine and Dentistry of New Jersey
2009 – 2013	Member, Scientific Advisory Board, US Food and Drug Administration
2013 – 2015	Council Delegate, Biological Sciences Section, American Associate for the Advancement of Science
2014 – present	Fellow, American Association for the Advancement of Science

C. Selected peer-reviewed publications (Selected subset from a total of 150+).

1. Xu, Y.F., Zhao, X., Glass, D.S., Absalan, F., Perlman, D.H., Broach, J.R., and Rabinowitz, J.D. (2012) Regulation of yeast pyruvate kinase by ultrasensitive allostery independent of phosphorylation. *Molecular Cell*, **48**:52-62

2. Petrenko, N., Chereji, R.V., McClean, M., Morozov, A.V., and Broach, J.R. (2013) Noise and interlocking signaling pathways promote distinct transcription factor dynamics in response to different stresses, *Mol Biol Cell*, **24**:2045-57.

3. Shor, E., Fox, C.A. and Broach, J.R. (2013) The environmental stress response regulates genetic mutation in yeast, *PLoS Genetics* **9**(8):e1003680.

4. Yi-Fan Xu, Fabien Létisse, Farnaz Absalan, Wenyun Lu, Ekaterina Kuznetsova, Greg Brown, Amy A. Caudy, Alexander F. Yakunin, James R. Broach, Joshua D. Rabinowitz (2013) Nucleotide degradation and ribosalvage in yeast, *Mol. Sys. Biol, **9**:665*.

5. Elfving N, Chereji RV, Bharatula V, Björklund S, Morozov AV, Broach JR (2014) A dynamic interplay of nucleosomes and Msn2 binding regulates kinetics of gene activation and repression following stress. *Nucleic Acids Res*. **42**: 5468-82.
6. Su, X., Broach, J.R., Connor, J., Gerhard, G., and Simmons, Z., (2013) Genetic Heterogeneity of ALS: Implications for Clinical Practice and Research, *Muscle and Nerve*, **49**:786-803

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
GLENN S. GERHARD	**Professor and Chair**
eRA COMMONS USER NAME **gsgerhard**	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Penn State University, University Park, PA	**B.S.**	**1982**	**Biochemistry**
Penn State College of Medicine, Hershey, PA	**M.D.**	**1986**	**Medicine**
Wistar Institute, Philadelphia, PA	**Postdoc**	**1986-1987**	**Cell Biology of Aging**
University of Pennsylvania, Philadelphia, PA	**Postdoc**	**1990-1992**	**Human Genetics**

A. Personal Statement

Amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease is a devastating neurological disease for which there is no effective therapy. Approximately 5-10% of cases are inherited and thus run in families, while a genetic basis for the remaining cases has not yet been determined. The primary objective of this project is to further define the genetic architecture of ALS. Our goal is identify new mutations and new genes associated with ALS. We established processes for consenting ALS patients and collecting biological samples (e.g., saliva, blood, etc.) and conducted whole exome sequencing on a large number of patients.

B. Positions and Honors

Positions and Employment

1986-1987	Postdoctoral Fellow, Cell Biology of Aging, Wistar Institute, Philadelphia, PA
1987-1990	Resident Physician, Pathology, Dartmouth-Hitchcock Medical Center, Hanover, NH
1990-1992	Postdoctoral Fellow, Human Genetics, University of Pennsylvania, Philadelphia, PA
1992-1994	Research Assistant Professor, Medical College of Pennsylvania, Philadelphia, PA
1994-1995	Clinical Fellow, Transfusion Medicine, University of Wisconsin, Madison, WI
1995-1999	Assistant Professor (Clinical), Department of Pathology, Penn State-Hershey, Hershey, PA
1996-1999	Assistant Director, Molecular Diagnostics Laboratory, Penn State-Hershey, Hershey, PA
1996-1999	Member, InterCollege Graduate Program in Genetics, Penn State-Hershey, Hershey, PA
1996-	Faculty Affiliate, Center for Developmental and Health Genetics, Penn State, Univ. Park, PA
1997-1999	Co-Director, ImmunoBiology Graduate Option, Penn State-Hershey, Hershey, PA

1999-2003	Assistant Professor (Research), Dept. of Pathology, Dartmouth Med. School, Hanover, NH
1999-2003	Assistant Dir., Molecular Genetics Diagnostics Lab., Dartmouth Med. School, Hanover, NH
2003-2012	Staff Scientist, Weis Center for Research, Geisinger Clinic, Danville, PA
2004-2012	Medical Director, Molecular Diagnostics Laboratory, Geisinger Clinic, Danville, PA
2003-2012	Director, Geisinger Clinic Genomics Core, Geisinger Clinic, Danville, PA
2012-2014	Professor, Dept. of Biochemistry and Molecular Biology, Penn State-Hershey, Hershey, PA
2012-2014	Professor, Dept. of Pathology, Penn State-Hershey, Hershey, PA
2012-2014	co-Director, Institute for Personalized Medicine, Penn State-Hershey, Hershey, PA
2014-	Professor and Chair, Department of Medical Genetics and Molecular Biochemistry, Temple University School of Medicine, Philadelphia, PA

Honors

2014 Penn State Hershey Innovation in Team Science Award

C. Selected Peer-reviewed Publications (Selected from over 100 peer-reviewed publications)

Most relevant to the current application

1. Su XW1, Broach JR, Connor JR, Gerhard GS, Simmons Z. Genetic heterogeneity of amyotrophic lateral sclerosis: implications for clinical practice and research. Muscle Nerve. 2014 Jun;49(6):786-803. doi: 10.1002/mus.24198. Epub 2014 Apr 8.

Additional recent publications of importance to the field

1. Wood GC, Still CD, Chu X, Susek M, Erdman R, Hartman C, Yeager S, Blosky MA, Krum W, Carey DJ, Skelding KA, Benotti P, Stewart WF, **Gerhard GS.** Association of chromosome 9p21 SNPs with cardiovascular phenotypes in morbid obesity using electronic health record data. *Genomic Med*. 2008 Jan;2(1-2):33-43.
   - Editorial: Yamada Y. The electronic health record as a primary source of clinical phenotype for genetic epidemiological studies. Genomic Med. 2008 Jan;2(1-2):5.
2. **Gerhard GS**, Chu X, Wood GC, Gerhard GM, Benotti P, Petrick AT, Gabrielsen J, Strodel WE, Still CD, Argyropoulos G. Next-generation sequence analysis of genes associated with obesity and nonalcoholic fatty liver disease-related cirrhosis in extreme obesity. *Hum Hered.* 2013;75(2-4):144-51. doi: 10.1159/000351719. Epub 2013 Sep 27. PubMed PMID: 24081230; PubMed Central PMCID: PMC3981063.
3. Matzko ME, Argyropoulos G, Wood GC, Chu X, McCarter RJ, Still CD, **Gerhard GS**. Association of ghrelin receptor promoter polymorphisms with weight loss following Roux-en-Y gastric bypass surgery. *Obes Surg.* 2012 May;22(5):783-90. doi:10.1007/s11695-012-0631-2. PubMed PMID: 22411573; PubMed Central PMCID: PMC3545394.
   - Selected as a Research Highlight for *Nature Reviews Gastroenterology and Hepatology*.: Greenhill C. *Nat Rev Gastroenterol Hepatol.* Apr 10;9(5):243 (2012). doi: 10.1038/nrgastro.2012.65.
4. PMID: 21311511Gorden A, Yang R, Yerges-Armstrong LM, Ryan KA, Speliotes E, Borecki IB, Harris TB, Chu X, Wood GC, Still CD, Shuldiner AR, **Gerhard GS**; GOLD Consortium. Genetic variation at NCAN locus is associated with inflammation and fibrosis in non-alcoholic fatty liver disease in morbid obesity. *Hum Hered.* 2013;75(1):34-43. doi:

10.1159/000346195. Epub 2013 Apr 10. PubMed PMID: 23594525; PubMed Central PMCID: PMC3864002.

5. Rinella ES, Still C, Shao Y, Wood GC, Chu X, Salerno B, Ostrer H**/Gerhard GS**. Genome-wide association of single-nucleotide polymorphisms with weight loss outcomes after Roux-en-Y gastric bypass surgery. *J Clin Endocrinol Metab.* 2013 Jun;98(6):E1131-6. doi: 10.1210/jc.2012-3421. Epub 2013 Apr 30. PubMed PMID: 23633212; PubMed Central PMCID: PMC3667258.
6. **Gerhard GS**, Styer AM, Strodel WE, Roesch SL, Yavorek A, Carey DJ, Wood GC, Petrick AT, Gabrielsen J, Ibele A, Benotti P, Rolston DD, Still CD, Argyropoulos G. Gene expression profiling in subcutaneous, visceral and epigastric adipose tissues of patients with extreme obesity. *Int J Obes (Lond).* 2014 Mar;38(3):371-8. doi: 10.1038/ijo.2013.152. Epub 2013 Aug 16. PubMed PMID: 23949615; PubMed Central PMCID: PMC3925764.
7. Parihar A, Wood GC, Chu X, Jin Q, Argyropoulos G, Still CD, Shuldiner AR, Mitchell BD, **Gerhard GS**. Extension of GWAS results for lipid-related phenotypes to extreme obesity using electronic health record (EHR) data and the Metabochip. *Front Genet.* 2014 Aug 5;5:222. doi: 10.3389/fgene.2014.00222. eCollection 2014. PubMed PMID: 25147553; PubMed Central PMCID: PMC4123014.
8. DiStefano, J., Kingsley, C, Wood, GC, Chu, X, Argyropoulos, G, Still, C, Doné, S, Legendre, C. Tembe, W, and **Gerhard, GS**. Genome-wide analysis of hepatic lipid content in extreme obesity. *Acta Diabetologica*, 2014. Sep 23. [Epub ahead of print] PMID: 25246029

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Kathryn Elizabeth Sheldon

eRA COMMONS USER NAME (credential, e.g., agency login): kathrynesheldon

POSITION TITLE: Research Project Manager 2

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
San Francisco State University, San Francisco, CA	BSc	05/99	Biology
University of Pittsburgh, Pittsburgh, PA	PhD	12/05	Molecular, cellular and developmental biology
University of Pittsburgh, Pittsburgh, PA	Postdoctoral Training	08/07	Mechanism of alternative splicing
University of Pittsburgh, Pittsburgh, PA	Postdoctoral Training	06/12	Regulation of transcription initiation

Please refer to the Biographical Sketch sample in order to complete sections A, B, C, and D of the Biographical Sketch.

A. Personal Statement

The goal of the proposed research is to discover novel rare and common gene variants relevant to amyotrophic lateral sclerosis (ALS). In particular, we plan to use exome sequencing to identify sequence variation in a large, well-documented clinical cohort here at Pennsylvania State University College of Medicine in Hershey, PA. I possess the expertise, leadership, and motivation required to successfully contribute to the proposed work. My graduate and postdoctoral training has provided me with the skill set required to accomplish large genomic based research projects. In particular, I have transferred molecular biology techniques to the application of exome library preparation, using either amplification or solution capture methods. As a laboratory instructor at CMU, I guided 18 undergraduates through mycobacteriophage purification and DNA isolation required for shotgun sequencing at the Joint Genome Institute. This research experience provided me a knowledge base that expanded into the dynamic field of next generation sequencing. Variant prioritization of affected individuals will inform the design of functional analyses of candidates in *Saccharomyces cerevisiae*, zebrafish, or mouse model systems. My experience in yeast genetics as a graduate student will aid in screening of potential causal variants in this or other model systems. The results from this study will aid in the goal of personalizing medicine and drug discovery. Genetic variants identified and confirmed in ALS patients may inform physicians on disease course which can be disclosed to patients. Moreover, clinical trials may be informed from drug discovery screens using functionally relevant genetic variants from this study as treatment options for ALS patients are lacking.

B. Position and Honors

Research and Professional Experience

2006 – 2007	Postdoctoral Fellow, Department of Biological Sciences, University of Pittsburgh, Pittsburgh, PA
2008 – 2009	Special Faculty Teaching Appointment, Carnegie Mellon University, Pittsburgh, PA
2009 – 2012	Postdoctoral Fellow, Department of Microbiology and Molecular Biology, University of Pittsburgh, PA
2012 – 2014	Research Associate, Department of Biochemistry and Molecular Biology, Pennsylvania State University College of Medicine, Hershey, PA
2014 -	Research Project Manager, Institute for Personalized Medicine, Pennsylvania State University College of Medicine, Hershey, PA

Honors

2013	Judith Bond Travel Award, Department of Biochemistry and Molecular Biology, Pennsylvania State University College of Medicine

C. Selected Peer-reviewed Publications

1. Squazzo, S.L., Costa, P.J., Lindstrom, D.L., Kumer, K.E., Simic, R., Jennings, J.L., Link, A.J., Arndt, K.M., and Hartzog, G.A. The Paf1 complex physically and functionally associates with transcription elongation factors in vivo. EMBO J. 2002; 21: 1764-1774. (PMID: 11927560)

2. Sheldon, K.E., Mauger, D.M., and Arndt, K.M. A requirement for the *Saccharomyces cerevisiae* Paf1 complex in snoRNA 4' end formation. Mol Cell. 2005; 20: 225-236. (PMID: 16246725)

3. Pope, W.H., Jacobes-Sera, D., Russell, D.A., Peebles, C.L., Al-Atrache, Z., …, Sheldon, K.E., *et al*. PLoS One. 2011; 6(1): e16329. (PMID: 21298013)

4. Sheldon, K.E., Shandilya, H., Kepka-Lenhart, D., Poljakovic, M., Ghosh, A., and Morris, S.M. Jr. Shapting the murine macrophage phenotype: IL-4 and cyclic AMP synergistically activate the arginase I promoter. J Immunol. 2013; 191(5): 2290-2298. (PMID: 23913966)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Lisa (Weis) Schneper

eRA COMMONS USER NAME (credential, e.g., agency login): SCHNEPEL

POSITION TITLE: Research Associate

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Boston College, Chestnut Hill, MA	BSc	05/1989	Biology
University of Medicine and Dentistry of NJ	PhD	05/1997	Biochemistry
Princeton University, Princeton, NJ	Postdoctoral Training	06/1997-06/2005	*S. cerevisiae* signal transduction

A. Personal Statement

The goal of the project is to identify rare variants associated with amyotrophic lateral sclerosis (ALS). I have a broad background in biochemistry, molecular biology, and analysis of large datasets that will allow me to successfully contribute to the project. I have utilized microarray technology to analyze genome wide transcriptional changes in the yeast *Saccharoymyces cerevisiae* in response to nutrient deprivation. I have also designed experiments to utilize 454 sequencing to characterize the microbiome of patients with cystic fibrosis or chronic obstructive pulmonary disorder. Since joining Penn State, I have been actively involved in analyzing whole genome sequencing data from a cohort of seven families with monozygotic twins, at least one having been diagnosed with autism spectrum disorder, and validating candidate associated variants. I have also been actively analyzing whole exome sequencing data and genotype array data from individuals with ALS and their parents to identify potential causative polymorphisms and copy number variants. Manuscripts describing these findings are in preparation.

B. Position and Honors

Research and Professional Experience

2001 - 2005 Postdoctoral Fellow/ Research Scientist, Department of Molecular Biology, Princeton University, Princeton, NJ

2005 - 2006 Assistant Professor, Columbus State University, Columbus, GA

2006 - 2007 Visiting Lecturer, Department of Biological Sciences, Florida International University (FIU), Miami, FL

2007 – 2012 Assistant Professor, Research Track, Department of Molecular Microbiology & Infectious Diseases, Herbert Wertheim College of Medicine, FIU, Miami, FL

2013 - present Research Associate, Department of Biochemistry and Molecular Biology, Pennsylvania State College of Medicine, Hershey, PA

2014 - present Professional Specialist, Department of Molecular Biology, Princeton University, Princeton, NJ

Honors

1990	Pre-doctoral Fellowship Honorable Mention, National Science Foundation
1990 - 1993	Pre-doctoral Fellowship, NJ Commission on Cancer Research (90-2138-CCR-00)
1998 - 2000	National Research Service Award, National Institutes of Health (5F32 GM19308)
2001	Captain Featherstone Award, Sonntag Institute of Cancer Research

C. Recent Peer-reviewed Publications

1: Caille O, Zincke D, Merighi M, Balasubramanian D, Kumari H, Kong KF,Silva-Herzog E, Narasimhan G, **Schneper L**, Lory S, Mathee K. Structural and functional characterization of *Pseudomonas aeruginosa* global regulator AmpR. J Bacteriol. 2014 Nov;196(22):3890-902. doi: 10.1128/JB.01997-14. Epub 2014 Sep 2. PubMed PMID: 25182487; PubMed Central PMCID: PMC4248820.

2: Jaric M, Segal J, Silva-Herzog E, **Schneper L**, Mathee K, Narasimhan G. Better primer design for metagenomics applications by increasing taxonomic distinguishability. BMC Proc. 2013 Dec 20;7(Suppl 7):S4. doi: 10.1186/1753-6561-7-S7-S4. Epub 2013 Dec 20. PubMed PMID: 24564926; PubMed Central PMCID: PMC4044206.

3: Kumari H, Murugapiran SK, Balasubramanian D, **Schneper L**, Merighi M, Sarracino D, Lory S, Mathee K. LTQ-XL mass spectrometry proteome analysis expands the *Pseudomonas aeruginosa* AmpR regulon to include cyclic di-GMP phosphodiesterases and phosphoproteins, and identifies novel open reading frames. J Proteomics. 2014 Jan 16;96:328-42. doi: 10.1016/j.jprot.2013.11.018. Epub 2013 Nov 28. PubMed
PMID: 24291602.

4: Balasubramanian D, **Schneper L**, Kumari H, Mathee K. A dynamic and intricate regulatory network determines *Pseudomonas aeruginosa* virulence. Nucleic Acids Res. 2013 Jan 7;41(1):1-20. doi: 10.1093/nar/gks1039. Epub 2012 Nov 11. Review. PubMed PMID: 23143271; PubMed Central PMCID: PMC3592444.

5: Balasubramanian D, **Schneper L**, Merighi M, Smith R, Narasimhan G, Lory S, Mathee K. The regulatory repertoire of *Pseudomonas aeruginosa* AmpC ß-lactamase regulator AmpR includes virulence genes. PLoS One. 2012;7(3):e34067. doi: 10.1371/journal.pone.0034067. Epub 2012 Mar 29. PubMed PMID: 22479525; PubMed Central PMCID: PMC3315558.

6: Sautter R, Ramos D, **Schneper L**, Ciofu O, Wassermann T, Koh CL, Heydorn A, Hentzer M, Høiby N, Kharazmi A, Molin S, Devries CA, Ohman DE, Mathee K. A complex multilevel attack on *Pseudomonas aeruginosa algT/U* expression and algT/U activity results in the loss of alginate production. Gene. 2012 May 1;498(2):242-53. doi: 10.1016/j.gene.2011.11.005. Epub 2011 Nov 9. PubMed PMID:
22088575.

7: Malladi VL, Sobczak AJ, Maricic N, Murugapiran SK, **Schneper L**, Makemson J, Mathee K, Wnuk SF. Substituted lactam and cyclic azahemiacetals modulate *Pseudomonas aeruginosa* quorum sensing. Bioorg Med Chem. 2011 Sep 15;19(18):5500-6. doi: 10.1016/j.bmc.2011.07.044. Epub 2011 Jul 28. PubMed PMID:

21855349; PubMed Central PMCID: PMC3171587.

8: Li CZ, Vandenberg K, Prabhulkar S, Zhu X, **Schneper L**, Methee K, Rosser CJ, Almeide E. Paper based point-of-care testing disc for multiplex whole cell bacteria analysis. Biosens Bioelectron. 2011 Jul 15;26(11):4342-8. doi: 10.1016/j.bios.2011.04.035. Epub 2011 Apr 28. PubMed PMID: 21592765.

Complete List of Publications in My Bibliography
http://www.ncbi.nlm.nih.gov/sites/myncbi/lisa.schneper.2/bibliography/40047542/public/?sort=date&direction=ascending