PI:	Title: A Prospective Study of Biochemical and Genetic Predictors of PCOS in High Risk Early Postmenarchal Girls	
Received: 02/12/2016	FOA:	Council: 10/2016
Competition ID: FORMS-C	FOA Title: Mentored Patient-Oriented Research Career Development Award (Parent K23)	
	Dual:	Accession Number:
IPF:	Organization:	
Former Number:	Department:	
IRG/SRG: CHHD-R	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 151,000 Year 2: 151,000 Year 3: 151,000 Year 4: 151,000	Animals: N Humans: Y Clinical Trial: N Current HS Code: 30 HESC: N	New Investigator: N Early Stage Investigator: N
Senior/Key Personnel:	*Organization:*	*Role Category:*

Reference Letters

Additions for Review

Updated Pages New Publications

OMB Number: 4040-0001
Expiration Date: 06/30/2016

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	**State Application Identifier**

1. TYPE OF SUBMISSION*

❍ Pre-application ● Application ❍ Changed/Corrected Application

4.a. Federal Identifier

b. Agency Routing Number

c. Previous Grants.gov Tracking Number

2. DATE SUBMITTED 2016-02-12

Application Identifier

5. APPLICANT INFORMATION

Organizational DUNS*:

Legal Name*:
Department:
Division:
Street1*:
Street2:
City*:
County:
State*:
Province:
Country*:
ZIP / Postal Code*:

Person to be contacted on matters involving this application

Prefix: First Name*: Middle Name: Last Name*: Suffix:

Position/Title:
Street1*:
Street2:
City*:
County:
State*:
Province:
Country*:
ZIP / Postal Code*:
Phone Number*: Fax Number: Email:

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)**

7. TYPE OF APPLICANT*

M: Nonprofit with 501C3 IRS Status (Other than Institution of Higher Education)

Other (Specify):

Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION*

● New ❍ Resubmission
❍ Renewal ❍ Continuation ❍ Revision

If Revision, mark appropriate box(es).

❍ A. Increase Award ❍ B. Decrease Award ❍ C. Increase Duration
❍ D. Decrease Duration ❍ E. Other *(specify)* :

Is this application being submitted to other agencies?* ❍Yes ●No What other Agencies?

9. NAME OF FEDERAL AGENCY*
National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER
TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
A Prospective Study of Biochemical and Genetic Predictors of PCOS in High Risk Early Postmenarchal Girls

12. PROPOSED PROJECT

Start Date* Ending Date*
09/01/2016 08/31/2020

13. CONGRESSIONAL DISTRICTS OF APPLICANT

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: First Name*: Middle Name: Last Name*: Suffix:

Position/Title:

Organization Name*:

Department:

Division:

Street1*:

Street2:

City*:

County:

State*:

Province:

Country*:

ZIP / Postal Code*:

Phone Number*: Fax Number: Email*:

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	$652,320.00
b. Total Non-Federal Funds*	$0.00
c. Total Federal & Non-Federal Funds*	$652,320.00
d. Estimated Program Income*	$0.00

16.IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

a. YES ❍ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:

DATE:

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR

❍ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● I agree*

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: First Name*: Middle Name: Last Name*: Suffix:

Position/Title*:

Organization Name*:

Department:

Division:

Street1*:

Street2:

City*:

County:

State*:

Province:

Country*:

ZIP / Postal Code*:

Phone Number*: Fax Number: Email*:

Signature of Authorized Representative*

Date Signed*

02/12/2016

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:K_23_cover_letter_2_5_16LT1009745755.pdf

424 R&R and PHS-398 Specific Table Of Contents

OMB Number: 4040-0010
Expiration Date: 06/30/2016

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:

Duns Number:
Street1*:
Street2:
City*:
County:
State*:
Province:
Country*:
Zip / Postal Code*:
Project/Performance Site Congressional District*:

File Name

Additional Location(s)

Funding Opportunity Number: PA-14-049. Received Date: 2016-02-12T14:39:00.000-05:00

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* ● **Yes** ❍ **No**

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ❍ Yes ● No

If YES, check appropriate exemption number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6

If NO, is the IRB review Pending? ● **Yes** ❍ **No**

IRB Approval Date:

Human Subject Assurance Number 00001011

2. Are Vertebrate Animals Used?* ❍ **Yes** ● **No**

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ❍ Yes ❍ No

IACUC Approval Date:

Animal Welfare Assurance Number

3. Is proprietary/privileged information included in the application?* ❍ **Yes** ● **No**

4.a. Does this project have an actual or potential impact - positive or negative - on the environment?* ❍ **Yes** ● **No**

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ❍ Yes ❍ No

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* ❍ **Yes** ● **No**

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* ❍ **Yes** ● **No**

6.a. If yes, identify countries:

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	K23_Project_Summary_2_8_16LT1009745741.pdf
8. Project Narrative*	K23_Narrative_ 2_8_2016LT1009745742.pdf
9. Bibliography & References Cited	Lit_Cited1009820831.pdf
10.Facilities & Other Resources	K23_Facilities__Other_Resources_Torchen_2_8_16LT1009745743.pdf
11.Equipment	K23_Equipment_ 2_8_16LT1009745744.pdf
12. Other Attachments	Authentication_of_Key_Resources_Plan1009745777.pdf List_of_References1009745778.pdf

Funding Opportunity Number: PA-14-049. Received Date: 2016-02-12T14:39:00.000-05:00

PROJECT SUMMARY

This career development award will allow to develop the experience and skill set required to achieve her long term goal of establishing an independent research program primarily focused on investigation of the developmental and genetic origins of polycystic ovary syndrome (PCOS). Through this work, hopes to translate her research findings into clinical practice in order to improve early prevention and treatment interventions for this disorder. If these goals are achieved, she will have a lasting impact on her scientific field and improve the clinical care of patients with PCOS.

Controversy regarding diagnosis of PCOS during early adolescence has delayed implementation of prevention and treatment strategies, so the impact of proposed work is significant. will use this award to enhance her skills in execution of physiologic protocols and to develop skills in statistical and molecular genetics. These skills will leave her well-positioned to successfully compete for independent funding in the next phase of her career. will achieve her training goals through a career development plan that consists of intensive mentorship, completion of a Master's Degree of Science in Clinical Investigation, participation in institutional scientific and career development seminars, and attendance and presentation at national meetings. Her primary mentor is an expert in clinical studies in PCOS, who has ongoing NIH support and an excellent record of mentorship. Her secondary mentors are a pediatric endocrinologist and international expert in reproductive physiology in childhood and adolescence, and a molecular and statistical geneticist focused on identification of genes important in the pathogenesis of complex genetic traits.

The overall goal of research strategy is to identify early clinical and genetic markers of PCOS in daughters of affected women and obese girls. Aim 1 will test the hypothesis that early adolescent postmenarchal PCOS daughters will have a distinct reproductive and metabolic phenotype characterized by ovarian hyperandrogenism, increased ovarian follicle count, and evidence for pancreatic β-cell dysfunction, which hyperandrogenic obese girls and control girls will lack. Aim 2 will test the hypothesis that early adolescent PCOS daughters with ovarian hyperandrogenism and increased ovarian follicle count will fulfill diagnostic criteria for PCOS at postmenarchal age three years, while hyperandrogenic obese girls will fail to meet these criteria. Aim 3 will test the hypothesis that a PCOS genetic risk score will predict the diagnosis of PCOS in this adolescent cohort.

PROJECT NARRATIVE

Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting 7 to 10% of reproductive-aged women worldwide. PCOS is associated with negative reproductive outcomes including subfertility and metabolic outcomes including type 2 diabetes and the metabolic syndrome. This project is designed to identify early clinical and genetic markers of PCOS in young girls at risk, a critical step toward development of early prevention and treatment approaches.

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FACILITIES AND RESOURCES

works within the Division of Endocrinology at the of (formerly), a new facility which opened in June of 2012 on the campus of . of is the teaching affiliate for the .

is the only freestanding hospital exclusively for children in Illinois. It is a 23-story, state-of-the-art, nationally-ranked hospital with 288 inpatient beds which offers the latest innovations in medical technology and research. Its 1,100 pediatric specialists, focusing on more than 70 specialties, treat the most critically ill kids in the area and provide care at 13 area locations.

is a major academic medical and research institution with innovative programs in biomedical research and medical education. The infrastructure at the medical campus supports multidisciplinary efforts to provide exceptional medical care and cutting-edge research. For the 2014-2015 academic year, researchers at were awarded over $402 million in sponsored research funding.

Office: has 150 sq. ft. of shared office space and shares administrative support with members of the Division of Endocrinology. Standard office equipment including photocopiers, fax machines, printers, computers, etc. is available.

Computer: has a PC electronically linked to publication-quality printers and PubMed. The PC includes computer software capable of word processing, data analysis (SAS 9.4), power calculation (PASS 2008), and production of graphs and slides (GraphPad Prism). External hard drives are in place for the backup of each computer. Additionally, computer support is available at all times to faculty and staff. personal PC and all other PCs used at and are encrypted and password protected for protection of patient information.

Clinical: maintains an active clinical practice within the Division of Endocrinology at of She spends one full day per week in the outpatient clinic located at the hospital in which she cares for patients with a variety of hormone-related conditions, including diabetes and disorders of growth, puberty, adrenal, pituitary and thyroid glands. She attends the inpatient endocrinology service 4 weeks per year and shares in overnight and weekend call with colleagues. She is actively involved in teaching medical students, residents, and fellows both in the outpatient and inpatient settings.

Clinical Research Unit: There is a dedicated Clinical Research Unit at where staff are familiar with metabolic and reproductive studies in children. The unit is staffed by trained research nurses and laboratory staff. The research laboratory is located adjacent to the unit and can process and store collected blood samples. Freezers (-80°Celsius) are located in the research lab for long-term storage of samples.

Center for Translational Imaging (CTI): CTI is research imaging facility. Equipment currently dedicated to research includes: 3T Siemens Prisma, 3T Siemens Trio, IR navigated TMS from Nexstim. Both Siemens 3T whole body magnets are 100% dedicated to research imaging. The state of the art technology allows the use of 102 different coils on 32 independent receiver channels (TRIO) or 64 channels (PRISMA). The magnetic field gradients for the TRIO are 40 mT/M while those of the PRISMA are 80 mT/m and both have the same slew rate of 200 mT/m/s.

Laboratory: has 500 sq ft of wet laboratory space on the 15th floor of the with two computer workstations and direct access to additional facilities such as cold rooms, equipment rooms, darkrooms, dishwashing/autoclave rooms, and conference rooms. The wet laboratory space will be used for sample processing, DNA extraction, glucose assays, and sample storage. dry laboratory space comprises 500 sq ft, which includes 4 clinical research staff offices. will have full access to these resources during her K23 support.

has 500 sq ft. of wet laboratory space on the 15th floor. Equipment includes thermal cyclers (384 well and 96 well, standard and gradient), power supplies, microcentrifuges, electrophoresis equipment etc. All equipment needed for molecular genetic and DNA polymorphism analysis is available. Darkroom facilities, autoclave and dishwasher are available as common equipment on the floor. also has access to a 377 ABI sequencer for genotyping and a 3100 ABI sequencer for DNA sequencing and STRP genotyping. Both sequencers are common equipment for the Division of Endocrinology. laboratory is adjacent to wet laboratory. will also have full access to these resources during her K23 support.

Clinical Population: has maintained a PCOS Registry which includes ~3,000 women with PCOS and ~1,000 reproductively normal control women. The Weight and Wellness Center at , a multidisplinary clinic for management of severe obesity in children and adolescents, performs ~475 patient visits annually. The Division of Endocrinology at completes ~10,000 patient visits a year. Each of these patient populations will be sources for subject recruitment.

Institutional Environment: There is a rich research environment at and the . There is ample opportunity for collaboration as the topics of early origins of metabolic disease are being explored by multiple researchers at our institution. The are dedicated to finding strategies to reduce metabolic disease and each center has contributed to past and current research studies.

The Center for Genetic Medicine (CGM), directed by , was founded in 2000 to facilitate the development of new genetic knowledge and its application to medicine, while improving public understanding of genetics. Today, CGM supports the genetic research of over 100 faculty members from 33 departments and three schools through their three core facilities and services, and also offers formal academic programs and public education.

The is funded by a Clinical and Translational Award (CTSA) from the NIH and supported by extensive institutional resources. is an integral hub for clinical and translational research enterprise. provides numerous resources and services for successful implementation of career development programs including grant writing seminars, data informatics resources, and formal didactic opportunities through the Master of Science in Clinical Investigation (MSCI) program, in which is enrolled.

Early Stage Investigator Support: has had extensive career development training, first as a supported clinical investigator under the mentorship of an experienced clinical researcher, and more recently, as a BIRCWH K12 Scholar. During this time period, she began work towards a Master of Science degree in Clinical Investigation at the Graduate School at She has and continues to participate in the numerous resources available through including bimonthly meetings for all K grant awardees, grant writing seminars, and data informatics resources. Additionally, she participates in the faculty development series offered to the members of the Department of Pediatrics.

Departmental Support: The Department of Pediatrics has demonstrated an investment in the success of physician scientist career trajectory. Since her faculty appointment in 2013, she has been provided with protected research time (currently 75% research/25% clinical) and the resources necessary to carry out her research objectives. She has a number of career development mentors within the Department who are committed to her success as a clinical researcher.

MAJOR EQUIPMENT

There is no equipment beyond that described in the Facilities and Other Resources Section.

AUTHENTICATION OF KEY BIOLOGICAL AND/OR CHEMICAL RESOURCES

No biological or chemical resources will be utilized in this proposal.

LIST OF REFERENCES

The following persons with submit referee letters on my behalf:

1)

2)

3)

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator				
Prefix:	First Name*:	Middle Name	Last Name*:	Suffix:
Position/Title*:				
Organization Name*:				
Department:				
Division:				
Street1*:				
Street2:				
City*:				
County:				
State*:				
Province:				
Country*:				
Zip / Postal Code*:				
Phone Number*:	Fax Number:	E-Mail*:		
Credential, e.g., agency login:				
Project Role*: PD/PI		Other Project Role Category:		
Degree Type:		Degree Year:		
		File Name		
Attach Biographical Sketch*:		Bio_	pdf	
Attach Current & Pending Support:				

Funding Opportunity Number: PA-14-049 . Received Date: 2016-02-12T14:39:00.000-05:00

PROFILE - Senior/Key Person				
Prefix:	First Name*:	Middle Name	Last Name*:	Suffix:
Position/Title*:				
Organization Name*:				
Department:				
Division:				
Street1*:				
Street2:				
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State*:				
Province:				
Country*:				
Zip / Postal Code*:				
Phone Number*:	Fax Number:	E-Mail*:		
Credential, e.g., agency login:				
Project Role*: Other (Specify)		Other Project Role Category: Mentor		
Degree Type:		Degree Year:		
		File Name		
Attach Biographical Sketch*:		Bio1009820858.pdf		
Attach Current & Pending Support:		Other_Support1009820859.pdf		

PROFILE - Senior/Key Person				
Prefix:	First Name*:	Middle Name	Last Name*:	Suffix:
Position/Title*:				
Organization Name*:				
Department:				
Division:				
Street1*:				
Street2:				
City*:				
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State*:				
Province:				
Country*:				
Zip / Postal Code*:				
Phone Number*:	Fax Number:	E-Mail*:		
Credential, e.g., agency login:				
Project Role*: Other (Specify)		Other Project Role Category: Co-Mentor		
Degree Type:		Degree Year:		
		File Name		
Attach Biographical Sketch*:				
Attach Current & Pending Support:		K23_ Current_and_Pending_Support_2_3_16LT1009745769.pdf		

Funding Opportunity Number: PA-14-049 . Received Date: 2016-02-12T14:39:00.000-05:00

PROFILE - Senior/Key Person				
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Position/Title*:				
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Phone Number*:	Fax Number:		E-Mail*:	
Credential, e.g., agency login:				
Project Role*: Other (Specify)		Other Project Role Category: Co-Mentor		
Degree Type:		Degree Year:		
		File Name		
Attach Biographical Sketch*:		Bio_ pdf		
Attach Current & Pending Support:		Other_Support1009820861.pdf		

PROFILE - Senior/Key Person				
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State*:				
Province:				
Country*:				
Zip / Postal Code*:				
Phone Number*:	Fax Number:		E-Mail*:	
Credential, e.g., agency login:				
Project Role*: Other (Specify)		Other Project Role Category: Other Significant Contributor		
Degree Type:		Degree Year:		
		File Name		
Attach Biographical Sketch*:		Bio1009820864.pdf		
Attach Current & Pending Support:				

OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

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:

eRA COMMONS USER NAME:

POSITION TITLE:

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY

A. Personal Statement

My area of interest is in early origins of polycystic ovary syndrome (PCOS), which I have explored through investigations of metabolic and reproductive phenotypes of first degree relatives (FDRs) of affected women. Because PCOS is a highly heritable condition, the study of daughters of affected women during childhood and adolescence provides a unique opportunity to better understand the ontogeny of this syndrome. During my clinical fellowship in pediatric endocrinology, I investigated metabolic and reproductive phenotypes of PCOS daughters during early puberty and early childhood. Through these investigations, I identified new features of these phenotypes, including evidence for pancreatic β-cell dysfunction and hyperandrogenemia during peripuberty and increased 5α-reductase activity during early childhood.

Since joining the faculty at , I have continued studies of PCOS FDR phenotypes with my mentor, We reported differences in adrenal and gonadal steroidogenesis in brothers of women with PCOS. In this study we identified increased adrenal 3β-hydroxysteroid dehydrogenase activity, increased gonadal 17,20-lyase and decreased gonadal 17β-hydroxysteroid dehydrogenase activity, as well as increased gonadotropin responses to GnRH agonist stimulation in the PCOS brothers.

In July 2014, I was selected as a Building Interdisciplinary Research Careers in Women's Health (BIRCWH) Scholar in the Career Development in Women's Health (CDWH) program. As a BIRCWH scholar, I have continued my studies in the early origins of PCOS. I have started to examine distinctions in the early reproductive phenotypes of PCOS daughters compared to peripubertal obese girls, another group suggested to be at increased risk for PCOS. I found that unlike PCOS daughters, obese girls have decreased anti-Mullerian hormone levels during early puberty, suggesting they may lack an increase in ovarian follicles, a key feature of the PCOS reproductive phenotype. Most recently, I am performing dynamic endocrine testing to study the glandular sources of hyperandrogenemia in PCOS daughters and obese peripubertal girls. A K23 award will provide me with the opportunity to obtain more formal training in execution of physiologic research protocols in children and in statistical and molecular genetics, skills which I can apply to my investigations of the early origins of PCOS. Development of skills in these additional areas will position me to obtain independent research funding in the next stage of my career.

B. Research and/or Professional Experience

Employment

Honors

Professional Societies

C. Contribution to Science

1)

2)

3)

Complete List of Published Work in MyBibliography:

D. Research Support

Completed Research Support

None

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

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:

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

POSITION TITLE:

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

A. Personal Statement

I have a longstanding commitment to training and career development, having mentored almost 50 predoctoral, PhD, MD or MD, PhD trainees. I was a member of the training grant faculty of in Endocrinology, Diabetes and Metabolism at and a mentor on . I have been a member of the training faculty on Program in Endocrinology, Diabetes and Hormone Action since 2001 and became the in 2005. This program has an outstanding training record and was successfully competitively renewed in 2006 and 2011.

Further, as Principal Investigator of the Building Interdisciplinary Research Careers in Women's Health K12 program ( ) since 2008, I have overseen the implementation of its successful career development program. I have been of the NIH-supported Specialized Center of Research (SCOR) on Sex Differences since 2002. One of the missions of this SCOR is to train the next generation of scientists in this field. Both of these awards were successfully competitively renewed in 2012. I am also for Research of the Department of Medicine and one of my priorities is faculty career development. The first two publications below describe career development (1) and mentoring practices (2) created as part of the Building Interdisciplinary Research Careers in Women's Health K12 program ( ) that I direct. Because of my involvement in these diverse training initiatives as well as my experience as a mentor, I am excellently qualified to serve as a Primary Mentor for K23 application.

1.

2.

3.

4.

B. Positions and Honors

Positions and Employment

Other Experience and Professional Memberships

Honors

C. Contribution to Science (Citations Google Scholar)

1. Women with PCOS are at increased risk for type 2 diabetes and impaired glucose tolerance

In 1987, I was the first investigator to report that women with PCOS were at increased risk for glucose intoler- ance. In collaboration with my trainee, we found that ~30% of women with PCOS had impaired glucose tolerance and 10% of these young women already had T2D. These studies demonstrated that PCOS was an important metabolic disorder conferring a high risk for T2D. This research has had a transformative impact on the field. Screening for glucose intolerance is recommended in clinical guidelines for PCOS and PCOS is listed by the American Diabetes Association as a T2D risk factor.

a.

b.

c.

d.

2. PCOS is associated with a unique disorder of insulin action

We found that there was profound peripheral insulin resistance in PCOS, independent of obesity. Insulin re- sistance was secondary to a defect in post-binding insulin mediated-signal transduction due to increased consti- tutive serine phosphorylation of the insulin receptor and downstream signaling molecules. Members of the ex- tracellular signal–regulated kinase (ERK)1/2 signaling pathway contributed to this abnormal phosphorylation. This defect was selective affecting metabolic but not mitogenic signaling pathways in key insulin target tissues, such as skeletal muscle.

a.

b.

c.

d.

3. Mechanisms of association of insulin resistance and hyperandrogenism

Mine was among the first groups to investigate the mechanisms for the association between hyperinsulinemia and hyperandrogenism. Our findings indicated that insulin was an important reproductive hormone and that improving insulin sensitivity was a novel therapeutic modality for PCOS. This research has had a major impact on the field leading to widespread use of insulin sensitizing drugs for PCOS.

a.

b.

c.

d.

4. Male and female first-degree relatives have PCOS reproductive and metabolic phenotypes

In collaboration with my former trainee, we have shown that male as well as female relatives of affected women have both reproductive and metabolic features of PCOS. These findings are consistent with a genetic contribution to the reproductive and metabolic phenotypes characteristic of PCOS. Further, the meta- bolic and reproductive abnormalities are present in childhood and could potentially be used to predict future PCOS.

a.

b.

d.

e.

5. Mapping susceptibility genes for PCOS

We found the first reproducibly mapped PCOS susceptibility variant, a dinucleotide repeat mapping to an intron of the fibrillin-3 gene. We found three replicated genomewide significant PCOS susceptibility loci In the first genomewide association study in European ancestry PCOS. One of the novel loci was in the region of the gene for FSH beta subunit. This region was also significantly associated with LH levels in the quantitative trait analysis. These findings implicate alterations in gonadotropin secretion in the pathogenesis of PCOS.

a.

b.

c.

d.

Complete List of Published Work in MyBibliography:

D. Research Support

Ongoing Research Projects

Completed Research Support

OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

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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

A. Personal Statement

I have been a “bedside to bench” clinical investigator involved with research into pubertal disorders for over 40 years and continuous federal funding for research and training 1971-2011. Since discovering the elevated free testosterone and low sex hormone binding globulin blood levels of hirsute women in 1971, elucidating the role of androgen in normal and abnormal female reproductive endocrinology has been my primary research interest. Our development of the gonadotropin releasing hormone (GnRH) agonist test of pituitary-ovarian function identified the characteristic steroidogenic dysfunction of polycystic ovary syndrome (PCOS), which was instrumental in identifying that the essence of this disorder is functional ovarian hyperandrogenism. Our discovery that insulin and insulin-like growth factor I up-regulate the thecal androgenic response to luteinizing hormone was a key step in developing our widely accepted hypothesis that steroidogenic dysregulation underlies the ovarian and adrenal dysfunction of PCOS. Subsequently, we identified type 5 17ß-hydroxysteroid dehydrogenase as the ovarian testosterone-forming enzyme and then demonstrated a unique transcriptional link between the regulation of this enzyme and adiposity by insulin (1). We also discovered the essential role of peroxisome proliferator-related receptors in sebaceous gland development (2). Optimization of estrogen replacement therapy, which has been an interest of mine since discovery of physiologic role of plasma estradiol in growth at puberty (3) and subsequent demonstration that early very low dose estrogen replacement therapy optimizes growth in response to growth hormone treatment (4). Other research interests include the diagnostic use of GnRH agonists in pubertal disorders. I have also become active in Pediatric Endocrine Society quality improvement efforts. I continue to be an educator, focusing particularly on post-doctoral research training and mentoring.

1.

2.

3.

4.

B. Positions and Honors

Honors:

C. Contribution to Science

1. Discovery and elucidation of relationship of plasma free testosterone to hirsutism.

In 1968 at the completion of my training, measurement of plasma testosterone in women required 50cc blood for assay by complex double isotope derivative dilution techniques, clearly impractical for study of childhood androgenic disorders, and androgen status was ordinarily estimated from urinary 17-ketosteroid urinary excretion. I developed a new post-chromatographic competitive protein binding (CPB) assay for plasma testosterone that was 5-fold more sensitive, but proved to be only slightly better at identifying the apparent hyperandrogenism of hirsute women. That prompted me to develop the first practical assay for plasma free testosterone and to demonstrate that it was usually elevated in hirsute women, even if the total testosterone was normal, because the plasma SHBG binding capacity was significantly low (a). In a series of studies, a) the total testosterone CPB methodology was ultimately supplanted by specific radioimmunassay and b) the initial "free testosterone index" determined by the "reverse CPB" technique was put on a sound physicochemical basis with the collaboration of a trainee (b). The normal range thus established remains the norm to this day. These studies indicated that hirsutism, particularly moderately severe hirsutism, usually indicates a hyperandrogenic disorder. Serum free testosterone is now uniformly recognized as the best single indicator of female hyperandrogenism.

These studies laid the groundwork for then discovering that a) hirsute oligomenorrheic women differed from hirsute eumenorrheic women in having subnormal suppression of plasma free testosterone by dexamethasone in spite of normal suppression of other adrenal secretions, which was the basis for the later use of this test to define functional ovarian hyperandrogenism (FOH), and b) serum androgens were not tightly regulated by the female neuroendocrine system (c). Later our research group showed that women with clinical features of polycystic ovary syndrome (PCOS) did not necessarily have abnormal ovarian histology in spite of having biochemical evidence of FOH (d). These studies laid the groundwork for our current understanding of PCOS, further discussed below.

a)

b)

c)

d)

2. Discovery that adrenarche represents a change in the adrenal secretory response to ACTH.

The “puberty of the adrenal gland” whereby it begins secreting increasing amounts of androgen in mid-childhood has long been of mysterious origin. In 1970, it was thought to result from a putative pituitary adrenal androgen-stimulating hormone. After adapting my new testosterone assay to the assay of the major steroidogenic intermediates in androgen formation, I discovered that children with “premature adrenarche” had a characteristic pattern of steroid secretion that was glucocorticoid-suppressible (a) and differed from that elicited by prolonged ACTH stimulation (b). These studies indicated that adrenarche could be accounted for by a change in the pattern of adrenal secretion in response to ACTH. These studies are consistent with the subsequent demonstration that adrenarchal changes result from the unique pattern of steroidogenic enzyme expression of the developing adrenal zona reticularis.

In the 1980s, it was widely thought that typical adult adrenal hyperandrogenism, which is indicated by an elevated dehydroepiandrosterone (DHEA) level, was due to non-classic 3ß-hydroxysteroid dehydrogenase (3ßHSD) deficiency. We doubted this and demonstrated that the pattern of steroid secretion in such women was more often compatible with an exaggeration of adrenarche than 3ßHSD deficiency (c). We subsequently showed that hyperandrogenic women with elevated DHEA responses to ACTH typically lacked evidence of ovarian 3ßHSD deficiency; rather most had evidence of increased P450c17 activities (d). This suggested that functional adrenal hyperandrogenism is usually related to the functional ovarian hyperandrogenism of PCOS. It is currently thought that premature adrenarche is sometimes the first indication of the steroidogenic dysfunction of PCOS.

a)

b)

c)

d)

3. Development of the GnRH agonist test of combined pituitary-gonadal function.

In the 1980s I began to work on developing a method to test the coordinated steroidogenic function of the ovarian follicle. GnRH constant infusion for 4 hr had not proved satisfactory, then GnRH became scarce for diagnostic and research purposes. When GnRH agonists became available for research on their chronic use to treat central precocious puberty, I utilized their early agonistic effect to develop a new diagnostic test for the function of the pituitary-gonadal axis. I then put together a group to study the pituitary-gonadal axis in children and adult women and men. We demonstrated in women that the GnRH agonist nafarelin elicited a gonadotropin surge peaking at 4 hr that was followed by a consistent rise in plasma estradiol 12-20 hr later. Studies in normal and PCOS women showed PCOS to have an abnormal pattern of steroid secretion (a). The GnRH agonist test discriminated between gonadotropin deficiency and delayed puberty in teenage boys (b), and we showed maturational changes during puberty in boys and girls with disturbances of puberty. We subsequently switched to evaluation of a commercially available GnRH agonist, for which we published normal reference ranges for the GnRH agonist test in adults. After clearing regulatory hurdles (*45 CFR 46.407/21 CFR 50.54),* we ultimately established normal reference values for the GnRH agonist test and hormonal sleep test in peripubertal boys and girls (c,d). GnRH agonist testing is now in common usage.

a)

b)

c)

d)

4. Discovery of the nature of the ovarian androgenic dysfunction in polycystic ovary syndrome.

I developed the GnRH agonist test (above) in part to test the hypothesis that classic PCOS was due to aromatase deficiency, but the study group that I led discovered instead that the pattern of steroid responses—characterized by 17-hydroxyprogesterone hyper-responsiveness that was not associated with evidence of a steroidogenic block--was suggestive of a previously undescribed type of functional ovarian hyper-androgenism (FOH), which we attributed to abnormal regulation of P450c17. We then determined the frequency of this PCOS-type of steroidogenic response to GnRH agonist in a population of 40 successive hyperandrogenic women presenting to pediatric, medicine, and gynecology endocrinology clinics (a). The majority of hyperandrogenic women, particularly those with oligo-amenorrhea, proved to have the PCOS-type of FOH, though they often lacked LH elevation or ultrasonographically polycystic ovaries. These findings indicated that the pathophysiologic common denominator of hyperandrogenic amenorrheic women was usually FOH. Presentation of preliminary data from this study at the first NIH consensus conference on PCOS was an important consideration in the formulation of the 1992 set of NIH diagnostic criteria for PCOS. A series of further studies supported the proposal that dysregulation of steroidogenesis, particularly at the level of P450c17, underpinned FOH and that FOH was the essence of PCOS. It was proposed that FOH resulted from abnormal paracrine function of the ovary that could have an intrinsic basis or result from excess LH or insulin stimulation (b). These studies provided a new paradigm for understanding hyperandrogenic disorders in women. An intrinsic theca cell defect with constitutive overexpression of most steroidogenic enzymes was subsequently discovered by others to be typical of classic PCOS.

To test the possibility that FOH caused the amenorrhea of adolescents with well-controlled virilizing congenital adrenal hyperplasia, we performed ovarian androgenic function tests (c). While adrenal function was suppressed with dexamethasone, plasma free testosterone was elevated and LH and 17-hydroxyprogesterone responses to GnRH agonist were elevated. The findings were similar in an amenorrheic adolescent who had a congenital virilizing adrenal tumor removed in early infancy. We concluded that congenital virilizing disorders programmed the neuroendocrine axis to secrete excess LH at puberty and cause functional ovarian hyperandrogenism. Prenatal virilization has subsequently become perhaps the best animal model to study the developmental origin of PCOS.

We later identified type 5 17ß-hydroxysteroid dehydrogenase (17ß-HSD5) as the ovarian enzyme that formed testosterone from androstenedione (d). In collaboration with others we showed that its ovarian expression in humans is confined to theca cells. We then found, as noted above, that a transcription factor (KLF15) that mediates up-regulation of adipogenesis in response to insulin is also a member of the HSD17B5 co-regulator complex and is required for up-regulation of 17ß-HSD5 activity in response to insulin, thus linking the adipogenic and androgenic responses to insulin.

a)

b)

c)

d)

5. Discovery of insulin/IGF-1 amplification of LH signaling in normal theca cells by reversing homologous down-regulation of LH binding sites and the relationship of PCOS to type 2 diabetes mellitus.

Insulin resistance was established in the early 1980s to be associated with PCOS. After it was reported in 1986 that insulin stimulates androgen accumulation in incubations of ovarian stroma obtained from women with PCOS, we tested the hypothesis that insulin and insulin-like growth factors stimulated androgen secretion in normal theca cells. We established the normal LH-androgen dose-response relationship in rat theca cells grown in monolayer culture: we found that the initially linear dose-response relationship plateaued at higher LH doses, which was the first evidence for homologous desensitization to LH in theca cells (a). This finding suggests that desensitization protects against hyperandrogenism in response to LH. Insulin and IGF-1 were equipotent in left-shifting and up-regulating androgen responses to LH (1). Thus, insulin sensitizes the normal ovary to LH. We then found that homologous desensitization to LH was accompanied by loss of LH receptor binding sites on theca cells and that insulin/IGF-1 countered this effect (b). In normal women, using an ED50 human chorionic gonadotropin stimulation test, we found LH receptor desensitization to begin at half-maximal stimulation, as indicated by a slight but significant rise in 17-hydroxyprogesterone secretion, but no rise in androgens (3). However, functionally typical PCOS patients were hypersensitive to this means of LH receptor stimulation and had excessive rises of 17-hydroxyprogesterone and androgens (c).

After noting that most of our adolescent study patients had a parent with diabetes mellitus, often detected when asymptomatic by an oral glucose tolerance test, our group found that PCOS patients were not only insulin-resistant, they also had a pancreatic beta-cell defect that was typical of type 2 diabetes mellitus (d). This was the first indication of the relationship of PCOS to type 2 diabetes mellitus. My colleagues subsequently showed that this insulin secretory defect was related to diabetes in first-degree relatives, and they and others subsequently firmly established this relationship.

These studies indicate that homologous desensitization to LH is an important mechanism that protects the ovary from becoming hyperandrogenic and show a mechanism by which the hyperinsulinemia of type 2 (insulin-resistant) diabetes mellitus overrides this protective mechanism and sensitizes the ovary to LH.

a)

b)

c)

d)

Complete List of Published Work in MyBibliography:

D. Research Support:

Ongoing Research Support

None

Completed Research Support

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

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:

eRA COMMONS USER NAME:

POSITION TITLE:

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

A. Personal Statement

I am trained in Molecular Biology and Genetics and have greater than 20 years experience in applying statistical and molecular genetics methods to the identification of genes for complex traits and 19 years studying PCOS. These studies have resulted in the publication of 54 peer reviewed publications with over 2300 citations. Our research uses state-of-the-art genetic technology to identify POCS susceptibility loci. I was the primary author to identify and fine map the PCOS susceptibility locus mapping to chr.19p13.2 which remains one of the strongest PCOS susceptibility loci identified to date. We are also investigating the impact on PCOS susceptibility of the TGF beta signaling pathway, the inflammatory gene pathway, and obesity genes.

I have a strong commitment to the training and education of future scientists. To date I have mentored over 20 trainees at various levels of their academic development including eight graduate students and post docs, and more than 5 Endocrine fellows or residents for whom I have played an integral part in their training. I am also a member of the training faculty on the Program in Endocrinology, Diabetes and Hormone Action ( ), the Training Program in Reproductive Biology ( ), and of the MSTP Admissions Committee. Furthermore I have been part of the leadership of the Career Development in Women's Health (CDWH) Building Interdisciplinary Research Careers in Women's Health K12 program ( ) for the last 10 years and have served as the for the last six years. In this role I directly mentor all of our BIRCWH scholars. In addition to the general BIRCWH activities, I meet with each scholar at least quarterly to track their progress, discuss their goals, and plan their future career progression. As a wife and mother of two children I am also well qualified to provide mentorship on work-life balance issues. As evidence of my strength in this area I am invited to speak on work-life balance issues at national meetings (see C.1. below).

I have known for 3 years both in her role as a BIRCWH mentor and as a member of our PCOS research group and have been very impressed with her intelligence, insight and work ethic. Given our overlapping research interests in the pathology and genetics of PCOS and my experience with mentoring junior faculty, I feel uniquely qualified and honored to serve as mentor for on her K23 project.

B. Positions and Honors

Positions

Professional Memberships

Reviewing Service:

Editorial Service:

Honors

C. Contribution to Science

1. I am trained in Molecular Biology and Genetics and have more than 20 years experience in applying statistical genetics methods to the identification of genes for complex traits and 19 years studying PCOS. PCOS is the most common form of annovulatory infertility among reproductive age women and affects 5-10% young women. It is characterized by hyperandrogenemia and irregular or absent menses. It is also associated with an increased risk of obesity, insulin and diabetes and thus impacts the quality of life of women with PCOS throughout their lifespan. However, little is known about the etiology of PCOS. To elucidate the pathology of PCOS, our research uses state-of-the-art genetic methodology to identify POCS susceptibility loci. I was the primary author to identify and fine map the PCOS susceptibility locus mapping to chr.19p13.2 which remains one of the strongest PCOS susceptibility loci identified to date (et 1999; et al 2007 among others). We have also investigating the impact on PCOS susceptibility of the TGF beta signaling pathway, the inflammatory gene pathway, and obesity genes. These studies have shown that while PCOS shares phenotypic similarities with obesity and diabetes the underlying genetic cause appears to be different ( ). Population based studies carried out by us

( ) have demonstrated that the same major genetic loci contribute to PCOS in women of European ancestry as in women of Chinese ancestry. We published the first genome wide association study (GWAS) of PCOS in European ancestry women and are collaborating on a world-wide Meta Analysis of PCOS GWAS. Additional studies in our lab include the impact of rare genetic variation on the PCOS phenotype and the role of epigenetic variation on the PCOS phenotype.

a.

b.

c.

d.

2. Pregnancy is an insulin resistant state that places pregnant women are at an increased risk of becoming diabetic. Gestational diabetes places the mother at increased risk of developing diabetes after birth and places the baby at risk of adverse birth outcomes. The HAPO (Hyperglycemia and Adverse Pregnancy Outcome) cohort is a NIH-funded observational epidemiologic study that investigates the effect of varying degrees of glucose intolerance during pregnancy on adverse outcomes. The study aims to further our understanding of the levels of glucose during pregnancy that place the mother, fetus, and neonate at increased risk. I am collaborating with and and the HAPO collaborative group to identify genetic loci that impact maternal glycemia and fetal outcome. Findings from these studies have been critical in demonstrating that while some genes controlling maternal glycemia and fetal growth and adiposity are those same as those in adults, pregnancy specific factors are critical for both regulating maternal glycemia and fetal adiposity.

a.

b.

c.

d.

3. During my post- doctoral fellowship in the Laboratory of Neurogenetics, in NIH's National Institute on Alcohol Abuse and Alcoholism, I played a critical role in the development of both molecular and computational tools for genetic analysis. I assembled panels of short tandem repeat polymorphism for genome wide genotyping. We applied these linkage panels to carry out population phylogenetic studies of Native American and European populations and genetic linkage analysis of alcoholism. The linkage panel were subsequently refined and sold by Applied Biosystems for use of linkage mapping (ABI PRISM® Linkage Mapping Set). I also participated in the development of an Estimation Maximation algorithm for multi-locus haplotype generation. This approach has been cited in 400+ publications to date.
    a.
    b.
    c.

4. Continual scientific growth requires that new generations of highly qualified and competitive scientists be trained. I have a strong commitment to the training and education of these future scientists. I have mentored trainees at various levels of their academic development ranging from undergraduate students and through junior faculty. I am a member of the training faculty on the Program in Endocrinology, Diabetes and Hormone Action ( ), the Training Program in Reproductive Biology ( ) and of the MSTP Admissions Committee. Furthermore I have been part of the leadership of the Career Development in Women's Health (CDWH) Building Interdisciplinary Research Careers in Women's Health K12 program ( ) for the last 10 years and have served as the for the last six years. As a wife and mother of two children I am also well qualified to provide mentorship on work-life balance as well as academic issues. As evidence of my strength in this area I am invited to speak on work-life balance issues at national meetings (see below).
    a.
    b.
    c.
    d.

Complete List of Published Work in MyBibliography:

D. Research Support

Ongoing Research Support

Completed Research Support

OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

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:

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

POSITION TITLE:

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

A. Personal Statement

I am well suited to serve as a collaborator for this research project. I have been actively involved in magnetic resonance imaging research for the past 20 years focusing on novel imaging techniques throughout the abdomen and pelvis. I serve as the medical director of MR and am confident that we will be able to help provide the resources necessary for this study. In addition, I have the clinical expertise to evaluate the ovary for the study and we routinely perform at least 40 female pelvic MR exams per week for a variety of indications. I have worked extensively with inter-disciplinary teams in multiple disciplines including gastroenterology, hepatology, obstetrics-gynecology and surgical oncology. I have served as a collaborator in the past on several NIH grants and have published multiple peer reviewed publications on each project. I have been involved in female pelvic imaging including working with and in assessing patients with polycystic ovarian syndrome and served under the administrative core center for reproductive research.

1.

2.

3.

4.

B. Positions and Honors

Positions and Employment

Honors

C. Contribution to Science (publications selected from >150 manuscripts)

1. MR elastography as a novel noninvasive test to assess fibrosis

As a radiologist, one of my main interests has been to evaluate novel imaging techniques in the abdomen and pelvis. Fortunately, several years ago I obtained from of the , a novel MR imaging technique; MR elastography. Since that time, we have examined over 700 patients with liver disease and suspected fibrosis referred by our hepatologists. We have written several papers to confirm the utility of MRE to distinguish the different stages of fibrosis, to diagnose cirrhosis more accurately than with conventional anatomic imaging or diffusion-weighted imaging techniques, and to evaluate MR-guided liver biopsies in post liver transplant patients based on MRE results.

a.

b.

c.

d.

2. Diffusion weighted imaging as a functional imaging test in abdominal imaging

Diffusion weighted imaging, although widely used in neurologic imaging, has only more recently been used in abdominal and pelvic imaging. We have more recently routinely used diffusion weighted imaging in our practice and investigated its utility including the strengths and weaknesses of the technique in assessing pathology in a variety of diseases and organs. We worked with a variety of collaborators in multiple disciplines and correlated the results with pathology. I served as the principal investigator or mentor in many of these studies. I have also lectured at multiple meetings including our largest meeting, RSNA, on this topic.

a.

b.

c.

d.

3. Post therapy assessment using imaging

In addition to the contributions described above one of my main interests has been assessing novel therapy for cancer including Yttrium 90 radioembolization and chemoembolization. Working with a team of collaborators and world experts in interventional oncology, we helped describe the imaging appearance and benefits of this type of therapy in over 40 publications that I am an author. In addition, I have lectured at multiple national and international meetings and given grand rounds/visiting professor on this topic at several institutions on these topics.

a.

b.

c.

d.

Complete List of Published Work in MyBibliography:

D. Research Support

Ongoing Research Support

None

Completed Research Support

CURRENT AND PENDING SUPPORT

ACTIVE

PENDING

CURRENT AND PENDING SUPPORT

None

CURRENT AND PENDING SUPPORT

ACTIVE

PENDING

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

ORGANIZATIONAL DUNS*:

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization:

Start Date*: 09-01-2016 **End Date*:** 08-31-2017 **Budget Period: 1**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .						PD/PI	0.00	9			100,000.00	26,000.00	126,000.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **126,000.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Total Number Other Personnel					**Total Other Personnel**	
						Total Salary, Wages and Fringe Benefits (A+B)	**126,000.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

ORGANIZATIONAL DUNS*:

Budget Type*: ● Project ❍ Subaward/Consortium

Organization:

Start Date*: 09-01-2016 **End Date*:** 08-31-2017 **Budget Period: 1**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
Total Travel Cost	

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number:

Funding Opportunity Number: PA-14-049 . Received Date: 2016-02-12T14:39:00.000-05:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

ORGANIZATIONAL DUNS*:

Budget Type*: ● Project ❍ Subaward/Consortium

Organization:

Start Date*: 09-01-2016 **End Date*:** 08-31-2017 **Budget Period: 1**

F. Other Direct Costs	**Funds Requested ($)***
1. Materials and Supplies	25,000.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
Total Other Direct Costs	**25,000.00**

G. Direct Costs	**Funds Requested ($)***
Total Direct Costs (A thru F)	**151,000.00**

H. Indirect Costs

Indirect Cost Type	**Indirect Cost Rate (%)**	**Indirect Cost Base ($)**	**Funds Requested ($)***
1 . Federal Org Res MTDC	8	151,000.00	12,080.00
		Total Indirect Costs	**12,080.00**

Cognizant Federal Agency
(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	**Funds Requested ($)***
Total Direct and Indirect Institutional Costs (G + H)	**163,080.00**

J. Fee	**Funds Requested ($)***

K. Budget Justification*	File Name: Budget_Justification1009745780.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Funding Opportunity Number: PA-14-049 . Received Date: 2016-02-12T14:39:00.000-05:00

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

ORGANIZATIONAL DUNS*:

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization:

Start Date*: 09-01-2017 **End Date*:** 08-31-2018 **Budget Period: 2**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .						PD/PI	0.00	9			100,000.00	26,000.00	126,000.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **126,000.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Total Number Other Personnel					**Total Other Personnel**	
						Total Salary, Wages and Fringe Benefits (A+B)	**126,000.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

ORGANIZATIONAL DUNS*:

Budget Type*: ● Project ❍ Subaward/Consortium

Organization:

Start Date*: 09-01-2017 **End Date*:** 08-31-2018 **Budget Period: 2**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
Total Travel Cost	

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Funding Opportunity Number: PA-14-049 . Received Date: 2016-02-12T14:39:00.000-05:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2

ORGANIZATIONAL DUNS*:

Budget Type*: ● Project ❍ Subaward/Consortium

Organization:

Start Date*: 09-01-2017 **End Date*:** 08-31-2018 **Budget Period: 2**

F. Other Direct Costs	**Funds Requested ($)***
1. Materials and Supplies	25,000.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
Total Other Direct Costs	**25,000.00**

G. Direct Costs	**Funds Requested ($)***
Total Direct Costs (A thru F)	**151,000.00**

H. Indirect Costs

Indirect Cost Type	**Indirect Cost Rate (%)**	**Indirect Cost Base ($)**	**Funds Requested ($)***
1 . Federal Org Res MTDC	8	151,000.00	12,080.00
		Total Indirect Costs	**12,080.00**

Cognizant Federal Agency
(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	**Funds Requested ($)***
Total Direct and Indirect Institutional Costs (G + H)	**163,080.00**

J. Fee	**Funds Requested ($)***

K. Budget Justification*	File Name: Budget_Justification1009745780.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Funding Opportunity Number: PA-14-049 . Received Date: 2016-02-12T14:39:00.000-05:00

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

ORGANIZATIONAL DUNS*:

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization:

Start Date*: 09-01-2018 **End Date*:** 08-31-2019 **Budget Period: 3**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .						PD/PI	0.00	9			100,000.00	26,000.00	126,000.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **126,000.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Total Number Other Personnel					**Total Other Personnel**	
						Total Salary, Wages and Fringe Benefits (A+B)	**126,000.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

ORGANIZATIONAL DUNS*:

Budget Type*: ● Project ❍ Subaward/Consortium

Organization:

Start Date*: 09-01-2018 **End Date*:** 08-31-2019 **Budget Period: 3**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
Total Travel Cost	

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Funding Opportunity Number: PA-14-049 . Received Date: 2016-02-12T14:39:00.000-05:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3

ORGANIZATIONAL DUNS*:

Budget Type*: ● Project ❍ Subaward/Consortium

Organization:

Start Date*: 09-01-2018 **End Date*:** 08-31-2019 **Budget Period: 3**

F. Other Direct Costs	**Funds Requested ($)***
1. Materials and Supplies	25,000.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
Total Other Direct Costs	**25,000.00**

G. Direct Costs	**Funds Requested ($)***
Total Direct Costs (A thru F)	**151,000.00**

H. Indirect Costs

Indirect Cost Type	**Indirect Cost Rate (%)**	**Indirect Cost Base ($)**	**Funds Requested ($)***
1 . Federal Org Res MTDC	8	151,000.00	12,080.00
		Total Indirect Costs	**12,080.00**

Cognizant Federal Agency
(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	**Funds Requested ($)***
Total Direct and Indirect Institutional Costs (G + H)	**163,080.00**

J. Fee	**Funds Requested ($)***

K. Budget Justification*	File Name: Budget_Justification1009745780.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Funding Opportunity Number: PA-14-049 . Received Date: 2016-02-12T14:39:00.000-05:00

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 4

ORGANIZATIONAL DUNS*:

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization:

Start Date*: 09-01-2019 **End Date*:** 08-31-2020 **Budget Period: 4**

A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .					PD/PI	0.00	9			100,000.00	26,000.00	126,000.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **126,000.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Total Number Other Personnel					**Total Other Personnel**	
					Total Salary, Wages and Fringe Benefits (A+B)		**126,000.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 4

ORGANIZATIONAL DUNS*:

Budget Type*: ● Project ❍ Subaward/Consortium

Organization:

Start Date*: 09-01-2019 **End Date*:** 08-31-2020 **Budget Period: 4**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
Total Travel Cost	

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Funding Opportunity Number: PA-14-049 . Received Date: 2016-02-12T14:39:00.000-05:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 4

ORGANIZATIONAL DUNS*:

Budget Type*: ● Project ❍ Subaward/Consortium

Organization:

Start Date*: 09-01-2019 **End Date*:** 08-31-2020 **Budget Period: 4**

F. Other Direct Costs	**Funds Requested ($)***
1. Materials and Supplies	25,000.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
Total Other Direct Costs	**25,000.00**

G. Direct Costs	**Funds Requested ($)***
Total Direct Costs (A thru F)	**151,000.00**

H. Indirect Costs

Indirect Cost Type	**Indirect Cost Rate (%)**	**Indirect Cost Base ($)**	**Funds Requested ($)***
1 . Federal Org Res MTDC	8	151,000.00	12,080.00
		Total Indirect Costs	**12,080.00**

Cognizant Federal Agency
(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	**Funds Requested ($)***
Total Direct and Indirect Institutional Costs (G + H)	**163,080.00**

J. Fee	**Funds Requested ($)***

K. Budget Justification*	File Name: Budget_Justification1009745780.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Funding Opportunity Number: PA-14-049 . Received Date: 2016-02-12T14:39:00.000-05:00

BUDGET JUSTIFICATION

Key Personnel

Principal Investigator, (9.0 calendar months)
is an at the of and She will spend 75% effort in the career development and research activities as outlined in this application. will be responsible for the overall administration, direction, and execution of the project. Salary support of $100,000/year plus fringe benefits is requested for the four year duration of this award.

Fringe benefits are calculated at 26%.

Primary Mentor,
is the at As Primary Mentor, will share in responsiblity for all aspects of the candidate's career development, and provide supervision and technical assistance for clinical research protocol. will provide with additional research funding to supplement the research funds provided through this award. will also have access to lab space and technical support. has 500 sq ft of wet laboratory space in . will use this space for sample processing, DNA extraction, glucose assays, and sample storage. also employs a full time lab assistant and clinical research coordinator, who will assist with sample processing and subject recruitment, respectively. will regularly convene meetings and discuss progress with the co-mentors.

Co-Mentor,
is at located less than 10 miles from will provide with supervision and technical assistance for completion of her clinical research protocol. He will provide feedback on data analysis, presentation, and manuscript preparation. He will also provide with career development advice. will meet with at least quarterly and as otherwise necessary.

Co-Mentor,
is at will serve as primary genetics mentor for her K23 award. She will provide supervision and technical assistance with Aim 3 of proposal. will provide with access to her 500 sq ft of we laboratory space. This space will provide with access to all equipment needed for molecular genetic and DNA polymorphism analysis. She will meet with at least biweekly and as otherwise necessary.

Collaborator,
is Professor of Radiology at will provide readings for the MRI studies of ovarian morphology in the PCOS daughters, obese girls, and control girls as outlined in Aim 1 of proposal.

Project Support:
The request for project support, $25K annually, will be utilized for research related expenses, travel and education. A brief overview is provided below.

Material, Supplies, and Reagents: $6,100 Years 3 and 4
Disposable reagents and consumables needed for the project include Taqman primers and Master Mix needed for SNP genotyping and other general lab supplies.

CRU and Facility Expenses: $19,500 Years 1 and 2
CRU services will be utilized at for completion of the metabolic and reproductive phenotyping outlined in Aim 1 of proposal. Total CRU costs for this testing will be $434 per subject.

Fee for Service Lab Assays: $15,700 Years 3 and 4
Blood samples will be held until completion of all phenotyping studies and assayed during Years 3 and 4. Lab assays needed for the baseline metabolic and reproductive phenotyping studies and longitudinal follow up phenotyping will be performed at the (AMH, SHBG, leptin, adiponectin, C-peptide, insulin, LH, FSH, estradiol, DHEAS, 17-OHP, androstenedione: total cost $430 per subject) and at , laboratory of (testosterone by LC-MS, total cost $92 per subject).

Tuition, Masters of Science in Clinical Investigation, $4,000 Year 1, $2,800 Year 2
Tuition of $1,441/course after accounting for the employee reduced tuition benefit for Master's Program. Year 1 courses will include Presenting Research (MSCI 312), Data Management & Programming (EPI BIO 305), and Clinical Trials (PUB HLTH 446). Year 2 courses will include Writing and Peer Reviewing for Publication (MSCI 445) and Research Project (MSCI 499).

Travel: $1500 Years 1 and 2; $2,000 Years 3 and 4
A small amount of the Project Support funding will be utilized for travel to scientific meetings where updates on the project will be presented. Meetings will be selected with guidance from mentors, and may include the Annual Meeting of the Endocrine Society, the Pediatric Endocrine Society, and the American Society for Human Genetics.

Publication Costs: $1,200 Years 2 through 4
Requested for costs associated with manuscript publication.

Indirect Costs
Indirect costs are calculated at 8%.

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals ($)	
Section A, Senior/Key Person		504,000.00
Section B, Other Personnel		
Total Number Other Personnel		
Total Salary, Wages and Fringe Benefits (A+B)		504,000.00
Section C, Equipment		
Section D, Travel		
1. Domestic		
2. Foreign		
Section E, Participant/Trainee Support Costs		
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other		
6. Number of Participants/Trainees		
Section F, Other Direct Costs		100,000.00
1. Materials and Supplies	100,000.00	
2. Publication Costs		
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Other 1		
9. Other 2		
10. Other 3		
Section G, Direct Costs (A thru F)		604,000.00
Section H, Indirect Costs		48,320.00
Section I, Total Direct and Indirect Costs (G + H)		652,320.00
Section J, Fee		

Funding Opportunity Number: PA-14-049 . Received Date: 2016-02-12T14:39:00.000-05:00

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

1. Project Director / Principal Investigator (PD/PI)

Prefix:
First Name*:
Middle Name:
Last Name*:
Suffix:

2. Human Subjects

Clinical Trial? ● No ○ Yes
Agency-Defined Phase III Clinical Trial?* ○ No ○ Yes

3. Permission Statement*

If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)?

● Yes ○ No

4. Program Income*

Is program income anticipated during the periods for which the grant support is requested? ○ Yes ● No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

Budget Period*	Anticipated Amount ($)*	Source(s)*

Funding Opportunity Number: PA-14-049. Received Date: 2016-02-12T14:39:00.000-05:00

PHS 398 Cover Page Supplement

5. Human Embryonic Stem Cells

Does the proposed project involve human embryonic stem cells?* ● No ❍ Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Cell Line(s): Specific stem cell line cannot be referenced at this time. One from the registry will be used.

6. Inventions and Patents (For renewal applications only)

Inventions and Patents*: ❍ Yes ❍ No

If the answer is "Yes" then please answer the following:

Previously Reported*: ❍ Yes ❍ No

7. Change of Investigator / Change of Institution Questions

❑ Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix:

First Name*:

Middle Name:

Last Name*:

Suffix:

❑ Change of Grantee Institution

Name of former institution*:

PHS 398 Career Development Award Supplemental Form

OMB Number: 0925-0001

Introduction (if applicable)	
1. Introduction to Application (for RESUBMISSION applications only)	
Candidate Information	
2. Candidate's Background	K23_Candidate_s_Background_2_8_16LT1009745746.pdf
3. Career Goals and Objectives	Career_Goals_and_Objectives_K23_2_8_16LT1009745747.pdf
4. Career Development/Training Activities During Award Period	Career_Development_Plan_K23_LT_2_10_161009745748.pdf
5. Training in the Responsible Conduct of Research	K23_Training_in_RCR_2_8_16LT1009745749.pdf
6.Candidate's Plan to Provide Mentoring (as applicable)	
Statements of Support	
7. Plans and Statements of Mentor and Co-Mentor(s)	Mentors_Statements1009745762.pdf
8. Letters of Support from Collaborators, Contributors, and Consultants	LsOS1009745761.pdf
Environment and Institutional Commitment to Candidate	
9. Description of Institutional Environment	Inst_Environment1009820832.pdf
10. Institutional Commitment to Candidate's Research Career Development	Institutional_commitment1009820833.pdf
Research Plan	
11. Specific Aims	Spec_Aims1009820829.pdf
12. Research Strategy*	Research_Strategy1009820830.pdf
13. Progress Report Publication List (for RENEWAL applications only)	
Human Subject Sections	
14. Protection of Human Subjects	K23_Protection_of_Human_Subjects_K23_2_8_16LT1009745750.pdf
15. Inclusion of Women and Minorities	K23_INCLUSION_OF_WOMEN_AND_MINORITIES_2_8_16LT1009745751.pdf
16. Inclusion of Children	K23_INCLUSION_OF_CHILDREN_2_8_16LT1009745752.pdf
Other Research Plan Sections	
17. Vertebrate Animals	
18. Select Agent Research	
19. Consortium/Contractual Arrangements	
20. Resource Sharing Plan(s)	Resource_Sharing_Plan1009820865.pdf
Appendix (if applicable)	
21. Appendix	

Citizenship*:

- ● U.S. Citizen or noncitizen national
- Non-U.S. Citizen with temporary U.S. visa
- Permanent Resident of U.S. (If a permanent resident of the U.S., a notarized statement must be provided by the time of award)
- Permanent Resident of U.S. Pending

Funding Opportunity Number: PA-14-049. Received Date: 2016-02-12T14:39:00.000-05:00

CANDIDATE'S BACKGROUND

I am a pediatric endocrinologist seeking to establish an independent clinical research career focused on investigation of the early origins of polycystic ovary syndrome (PCOS). In the long term, I hope to translate my findings on the pathogenesis of PCOS into the development of novel prevention and early treatment approaches in girls at risk.

My interest in a career in clinical research developed fairly late in my medical training. After completing a chief resident year at , I planned for an academic career in the future, but one focused on patient care and medical education. During my first year of pediatric endocrinology fellowship at I became interested in the mechanisms involved in the relationship between hyperinsulinemia and hyperandrogenemia. My clinical experiences contributed to this interest, as I felt dissatisfied with the metabolic and reproductive outcomes experienced by my patients with disorders such as polycystic ovary syndrome (PCOS), premature adrenarche, and congenital adrenal hyperplasia. Therefore, I chose to focus on the early origins of PCOS for my fellowship research experience in hopes of having a positive impact on long term outcomes for these patients. Under the direction of my mentor, I began to study the early metabolic and reproductive phenotypes of daughters of women affected by PCOS, since these daughters are likely at increased risk for the disorder. It was during this fellowship research experience that I shifted my focus to pursue a career as a physician-scientist.

My first research contribution during fellowship was the novel finding that peripubertal PCOS daughters have decreased disposition index, a measure of pancreatic β-cell function and the most powerful predictor of type 2 diabetes risk. Indeed, these PCOS daughters are among the youngest children who have been identified with evidence of pancreatic β-cell dysfunction. I also found that testosterone levels were increased in these girls earlier in puberty than previously reported. I presented these findings during an oral session at the 94th Annual Meeting of the Endocrine Society in June 2012. There was also a longitudinal component to this study, during which we followed these subjects for up to three years to observe the evolution of these abnormalities. During the three years of follow up, I found that the decreased disposition index in the PCOS daughters was a persistent finding. I presented the data from the longitudinal component of this study during a featured poster presentation at the 95th Annual Meeting of the Endocrine Society in June 2013. I was first author on the manuscript reporting these findings, published in in October 2014.

I followed up on this work to test the hypothesis that altered androgen metabolism is present during early childhood in PCOS daughters. I measured excretion of steroid hormone metabolites in PCOS daughters compared to control girls, aged one to three years. I found that daughters of women with PCOS have evidence for increased 5α-reductase activity, a feature of the adult PCOS reproductive phenotype. 5α-reductase plays an important role in androgen metabolism, as it metabolizes testosterone to its more potent metabolite, dihydrotestosterone. Therefore, increased 5α-reductase activity may play a role in the pathogenesis of PCOS in these girls through increased exposure to androgen effects during critical developmental periods. I presented preliminary findings from this study at an oral session at the 95th Annual Meeting of the Endocrine Society in June 2013 and am first author on the manuscript describing our findings, which is in revision for the . These experiences introduced me to the excitement of discovery and the satisfaction of contributing to a scientific pursuit, shifting my focus towards a career as an independent investigator.

Since joining the faculty at , I have continued to mature as a scientist. In July 2014, I was selected as a K-12 recipient through the Building Interdisciplinary Careers in Women's Health (BIRCWH) program, funded through the National Institute of Child Health and Human Development. The BIRCWH program has provided me with the opportunity to begin to refine the skills I need to gain independence in my research pursuits. I have received more formal instruction in statistics, epidemiology, and scientific writing through my classes in the Master of Science of Clinical Investigation (MSCI) program at I have also participated in a number of career development seminars, including those on presentation skills, accountability, negotiation, and time management. A K23 award will allow me to develop the skills I need to apply statistical genetics in my investigations of the early origins of PCOS. This award will also allow me to continue to refine my skills in study design, statistical analysis, and scientific writing, preparing me to successfully compete for independent funding in the next phase of my career.

CAREER GOALS AND OBJECTIVES

My career goals are 1) to develop a research program primarily focused on investigation of the developmental and genetic origins of PCOS, and 2) to translate my research findings into clinical practice through improvement of prevention and early treatment approaches for this disorder. These goals are well-aligned with investigation of the early origins of health and disease, one of the key areas of interest for the National Institute of Child Health and Human Development.

1) Scientific Background

My research experience to date has been largely focused on investigation of early reproductive and metabolic phenotypes of daughters of women with PCOS. Through this work, I have identified novel features of these phenotypes, including increased 5α-reductase activity during early childhood and hyperandrogenemia and pancreatic β-cell dysfunction by the peripubertal years. I have also examined distinctions in the early phenotypes of PCOS daughters compared to peripubertal obese girls, another group suggested to be at increased risk for PCOS. I found that unlike PCOS daughters, obese girls have decreased anti-Mullerian hormone levels during early puberty, suggesting they may lack an increase in ovarian follicles, a key feature of the PCOS reproductive phenotype. Through these early research pursuits, I have learned about study design and execution, including regulatory issues related to clinical research in children. I have also learned statistical analyses and SAS programming for these data analyses.

In the next phase of my career development, I plan to refine the skills necessary for the development and implementation of research protocols in order to pursue more informative investigations of reproductive and metabolic physiology and pathophysiology. I also plan to obtain training in statistical and molecular genetics in order to integrate genetic studies into my investigation of this very heritable disorder.

2) Justification of Award

While my 18 months as BIRCWH K-12 scholar have allowed me to continue to develop the skills necessary for an independent clinical research career, my training remains incomplete. This K-23 award would allow me to develop and implement a clinical protocol in our pediatric clinical research unit, and provide me with additional training in statistical and molecular genetics. Finally, I will be able to establish an early adolescent cohort of girls at increased risk for PCOS who I will continue to follow in longitudinal observational studies and clinical trials. These accomplishments will leave me well positioned to successfully apply for independent funding by the end of Year 3 of my award.

CANDIDATE'S PLAN FOR CAREER DEVELOPMENT/TRAINING ACTIVITIES DURING AWARD PERIOD

I have designed a career development plan during which I will commit 75% of my professional time to career development and clinical research activities in reproductive and metabolic physiology and statistical and molecular genetics. This training will consist of 1) intensive mentorship, 2) formal coursework, 3) institutional education conferences, and 4) attendance and presentation at national meetings and seminars.

Intensive Mentorship

I have assembled an outstanding, multidisciplinary group that will provide mentorship as I transition towards independence. During the K23 award period, I will continue my relationship with as my primary mentor, but will develop new formal mentorship relationships with and to expand my training in statistical genetics and execution of physiologic research protocols in children, respectively.

(primary mentor) is the at the . She is a prominent investigator in the metabolic effects and genetic origins of PCOS and is currently the PI or co-PI on several NIH grants in this area, including an active grant, *Rare Genetic Variants in PCOS*, in which whole genome sequencing is being performed in families affected by PCOS to identify rare variants responsible for particular phenotypic features. has also maintained a PCOS Registry which includes more than 500 families with a PCOS index case as well as ~3,000 women with PCOS and ~1,000 reproductively normal control women for her genetic analyses of PCOS. A pending R01 received a priority score in the 6th percentile. She has successfully mentored numerous fellows, graduate students, and junior faculty including K12 and K23 awardees. I will continue to meet with weekly and as otherwise needed during the award period.

(co-mentor) is an . is an expert in molecular biology and human genetics, with a wealth of experience in applying statistical and molecular genetics methods to the identification of genes contributing to complex traits, including PCOS. I will continue to meet with weekly though our PCOS genetics meetings, and will meet one-on-one monthly or as needed to discuss my progress with Aim 3 of my project and my career development pertaining to statistical and molecular genetics.

(co-mentor) is an at is an internationally recognized expert in clinical studies of reproductive physiology and growth, with special emphasis on the role of androgens and estrogens in females. has held multiple NIH grants supporting this research throughout his career. He developed and validated the reproductive phenotyping testing protocol used in this proposal. He is also an expert in the ethical and technical aspects of completion of clinical research in children. I will meet with quarterly and as otherwise needed.

In addition to individual meetings with my mentors as described, I will meet with my entire mentorship team as a group annually to review my progress in my career development and research activities.

Formal Coursework

During the award period, I will complete the remaining coursework necessary to obtain a Master in Science of Clinical Investigation degree. Completion of this program will provide formal instruction in the skills necessary to achieve independence.

MSCI Courses	
MSCI 312 – Presenting Research	This course will provide an opportunity to present my research to other students and faculty in a larger setting. I will receive feedback on my presentation skills and practice giving informed and constructive feedback to my peers.
MSCI 445 – Writing and Peer Reviewing for Publication	This is an intensive, hands-on, advanced course in writing for publication in biomedical journals and how to be a successful peer reviewer. During the course I will prepare an article, respond to 2 peer review cycles, and at the conclusion of the course, to be ready to submit to a journal.
EPI BIO 305 – Data Management & Programming	This course will provide additional formal instruction on computer-based data management, statistical data processing, and programming using SAS systems.

PUB HLTH 446 – Clinical Trials	This course introduces commonly used designs for clinical trials, methods for randomization, blinding and sample size determination, choice of controls, collaborative/ multicenter trial requirements and operational issues, data management and data quality issues, interim analysis methods, critical review of clinical trial results, and statistical techniques for analyzing data. This critical formal instruction will prepare me to complete clinical trials for prevention and early treatment approaches in girls at risk for PCOS during my independent career.
MSCI 499 – Research Project	This course encompasses the development and presentation of a research project as the capstone project for the MSCI program. Students present a seminar on the project, prepare a grant application, and submit a manuscript for publication.

To obtain formal training in statistical genetics and to supplement the mentorship I will receive from I will attend two intensive courses on statistical genetics:

Courses in Statistical Genetics	
Summer Institute in Statistical Genetics, University of Washington School of Public Health - July 2017	The Institute consists of a series of two-and-a-half day workshops designed to introduce geneticists to modern methods of statistical analysis and to introduce statisticians to the statistical challenges posed by modern genetic data.
Short Course on Statistical Genetics & Genomics, University of Alabama at Birmingham – Date TBD	This short course equips students with the statistical genetic approaches necessary to expedite genomic discovery. The courses are taught by leading experts in statistical genetics/genomics. Each 5-day course provides substantial "hands-on" computer training that will effectively increase the number and the expertise of investigators who are pursuing genetic and genomic research.

Institutional Educational Conferences

Succeeding with your K Award (Third Mondays) Seminars – This monthly seminar series is designed to provide junior faculty the opportunity to present their work to a group of other early investigators and to receive feedback from the group. It is a group peer-mentoring experience moderated by **,**

.

**Grant Writing group, , ** – These weekly meetings are designed to provide support for junior faculty writing NIH grant proposals. In these meetings, small groups of faculty review and revise components of their grant proposals with input from other members of the group. The groups meet weekly for 2-3 months prior to the standard NIH grant deadlines. They are led by . I will attend these sessions while I prepare my R01 application during my third year as a K23 scholar.

Endocrine Seminar Series, Division of Endocrinology, Metabolism and Molecular Medicine, – Through this weekly seminar series, investigators and visiting scientists are invited to present their work. The seminar series is intended to update the Division on current advances in the field of endocrinology. I will present my research at these meetings annually during my K23 award period.

National Conferences

Annual Meeting of the Endocrine Society (ENDO)

Annual Meeting of the Pediatric Endocrine Society (PES)

Annual Meeting of the American Society of Human Genetics (ASHG)

National Symposia

Keystone Symposium: Sex and Gender Factors Affecting Metabolic Homeostasis, Diabetes and Obesity, March 19-22, 2017, Tahoe City, - The Keystone Symposia aim to connect scientists within disciplines to promote information exchange and the generation of new ideas. This meeting will focus on sex differences, the role of sex hormones, the systems biology of sex and the genetic contribution of sex chromosomes to metabolic homeostasis and diseases. will be a speaker at this meeting and will ensure that I am introduced to investigators in the field.

R01 Preparation

In the third year of the K23 award period, I will write an R01 proposal in order to continue my investigation of metabolic and reproductive outcomes in PCOS daughters and obese girls as they move into young adulthood. In the R01, I anticipate I will test the hypothesis that these distinct risk groups have differing responses to pharmacologic interventions for PCOS. I will also continue to expand my PCOS Child Registry: a prospective registry of young girls at risk for PCOS. Through this Registry, I will continue to study early metabolic and reproductive phenotypes in these girls, from infancy through adolescence.

Milestone Plan

CAREER DEVELOPMENT ACTIVITIES (3.0 person-months/year)	**Year 1**	**Year 2**	**Year 3**	**Year 4**
Mentor Meetings				
One-on-one mentor meetings: Weekly with monthly with quarterly with				
Annual mentorship committee meeting				
Formal Coursework				
MSCI Coursework				
University of Washington Summer Institute in Statistical Genetics				
Short Course on Statistical Genetics & Genomics, University of Alabama at Birmingham				
National Meetings				
PES				
ENDO				
ASHG				
Keystone Symposium - *Sex and Gender Factors Affecting Metabolic Homeostasis, Diabetes and Obesity*				
Institutional Seminars				
NUCATS Succeeding with your K Award Seminar				
Endocrine Seminar Series				
Department of Medicine New Investigator Career Enhancement Series				
NUCATS Grant Writing Group				
RESEARCH ACTIVITIES (6.0 person-months/year)				
Subject recruitment and data acquisition for baseline phenotype studies (Aim 1)				
Data analysis & Manuscript Publication: Baseline phenotypes (Aim 1)				
Longitudinal follow up: PCOS daughters, obese girls, controls (Aim 2)				
Analysis of PCOS genetic risk score in adolescent cohort (Aim 3)				
Data analysis & Manuscript Publication: Longitudinal follow-up (Aim 2) and Analysis of PCOS genetic risk score in adolescent cohort (Aim 3)				
R01 preparation, submission, revision				
CLINICAL DUTIES (2.4 person-months/year)				
2 half day clinics/week, shared call, 4 weeks inpatient service/yr.				
TEACHING (0.6 person-months/year)				
Teaching of fellows, residents, medical students in the clinic and ward. Participate in teaching conferences.				

TRAINING IN THE RESPONSIBLE CONDUCT OF RESEARCH

To meet the needs of advanced training in responsible conduct of research (RCR), a course for postdoctoral fellows and junior faculty was created – *Taking Responsibility for Responsible Conduct of Research*. I completed this course in the fall of 2014. The course is co-led by , , and in collaboration with the Office for Research Integrity. Between them there is extensive experience with RCR training. created and led a similar effort at the and has also led an empirical study of the influence of RCR courses on trainees. He also brings expertise learned from the *Survival Skills and Ethics* program run by the , and the *Teaching Research Ethics* program at the . Both and have experience leading clinical research studies and teaching the principles and practices by which such studies are conducted responsibly and ethically. also co-teaches the clinical research ethics course in the Masters of Science in Clinical Investigation program. To meet my once every four year requirement, I will take the RCR refresher course in 2018.

Format

The RCR course includes a combination of instructional styles including lecture and case study discussion (large and small group) and assigned discussions outside of class time.

Subject Matter

Topics covered explicitly include: Types of Misconduct and the Processes for Handling Misconduct, Mentoring and Lab Management, Data Ownership and Management, Conflict of Interest, Peer Review, Authorship, Research Using Animal and Human Subjects, and Collaborative Science. Contemporary ethical issues are covered with these sessions as well as in a culminating session where the group decides on one or two most current topics to discuss. The role of the scientist as a responsible member of society, as well as the societal impact of scientific research, are themes that are woven into many of the other topics that are treated more explicitly.

Faculty Participation

Due to the large number of faculty mentoring NIH-funded fellows, involving them all in a meaningful way in traditional course instruction as speakers, course directors, or discussion leaders is not practical. Instead, all pre-doctoral and postdoctoral RCR courses at require trainees to have one-on-one discussions with their mentors about a minimum of two RCR topics covered in the course. Trainees are required to submit a written summary/reflection of each conversation and to relate it to ideas that are discussed in class. For the written assignment, the student is expected to present this conversation in a way that relates to what had been discussed in class regarding professional norms and practices. This approach compels faculty to engage with their advisees on RCR topics in a very personal way, thereby enhancing the relevancy of the training for everyone involved, and extending RCR from the classroom to everyday life in research groups.

Duration and Frequency of Instruction

The postdoctoral course meets for 90 min per week, once a week, for 11 weeks – i.e. contact time ~ 15 hours.

Career-Stage Appropriate Instruction

The postdoctoral course differs from predoctoral courses in its emphasis on helping fellows and junior faculty learn the skills to mentor and become responsible for training their own research teams in RCR. Although formal RCR training is important, RCR is being 'taught' informally day in and day out. The focus is on guiding participants toward taking responsibility for those who will be looking to them for guidance. Extra attention is also given to the many nuances and complexities related to conflicts of interest, including non-monetary professional conflicts of interests scientists encounter more frequently than the highly publicized conflicts of financial interests.

February 8, 2016

Re: MD, K23 proposal, *A Prospective Study of Biochemical and Genetic Predictors of PCOS in High Risk Early Postmenarchal Girls*

Dear Review Committee:

Candidate

I am writing to express my enthusiasm for and commitment to serving as on her NIH K23 Mentored Career Development Award. I have known since 2011 when she joined my research group for her fellowship research experience. She has continued to work with me since being appointed to the faculty in September 2013. plans to build on the research theme she developed during this time on the developmental origins of polycystic ovary syndrome (PCOS). Specifically, she has discovered that the daughters of affected women (PCOS-d) have alterations in steroid hormone metabolism in early childhood. Further, they have elevations in circulating testosterone and anti-Müllerian hormone levels as well as evidence for pancreatic β-cell dysfunction by early puberty. Most recently, she has discovered that peripubertal obese girls (Ob-g) have similarly increased circulating testosterone levels compared to PCOS-d, but that they lack increases in anti-Müllerian hormone levels, another key feature of PCOS. These latter findings suggest the PCOS-d are phenotypically distinct from girls with obesity *per se*.

K23 proposal will investigate a scientific question of tremendous clinical relevance – *Which at risk girls will progress to PCOS?* She will accomplish this by examining, in PCOS-d and Ob-g with hyperandrogenemia, biochemical and genetic markers in the two years post-menarche when a formal diagnosis of PCOS cannot be made by the current diagnostic criteria. She will then follow these girls longitudinally for two years to determine which girls develop PCOS. If the Aims are achieved, this research will have a sustained and lasting impact on the field by identifying biomarkers for PCOS that will enable disease prediction and prevention strategies. This research will also substantially enhance skills as a physician-scientist and her progress towards a career as an independent investigator on the developmental origins of PCOS.

is a dedicated young investigator and is among the very best trainees I have mentored. combines exceptional clinical skills with a probing scientific mind. She has sought to establish herself in a minimally studied but critical area of research. She has already acquired many of the skill sets necessary for a career as a physician-scientist. She has been very productive given the complexity of the clinical studies she has conducted, including a longitudinal study with 2-years of follow-up. She has two original peer-reviewed publications in high impact journals. She has two additional manuscripts in revision for *&* , respectively. She has several more publications in preparation. I am confident that with her continued work as a K23 scholar, she will be ideally positioned to compete for independent funding by completion of her K23 award period.

Mentor's Qualifications

My research career has focused on elucidating the mechanisms of the metabolic and reproductive abnormalities in PCOS. We were the first to show that affected women had a unique disorder of insulin action and were at markedly increased risk for type 2 diabetes. My research group pioneered the treatment of the syndrome with insulin-sensitizing drugs. We discovered that hyperandrogenemia was a cardinal reproductive endophenotype in the first-degree relatives of affected women, including men and non-reproductive age women. We have had an NIH-supported *Specialized Center of Research on Sex Differences* (

) since 2002 investigating the overarching hypothesis that genetic variation leading to hyperandrogenemia causes the phenotypic features of PCOS by androgen programming *in utero* and at critical developmental windows postnatally. Recently, we were the first group to map PCOS susceptibility loci in affected women of European ancestry by genome-wide association scans (GWAS). research to date has been independent but complementary to my research program.

I have mentored approximately 50 trainees, a number of whom have established careers as successful independent investigators, for example and . This mentoring experience has included serving as a primary or secondary mentor on several K-series career development awards. Further, I have considerable experience in career development program leadership. I have been of the Program in Endocrinology, Diabetes and Hormone Action ( ) since 2005 and the since 2008. I am also and one of my priorities is faculty career development.

Based on my research expertise and mentoring experience, I am eminently qualified to serve as Primary Mentor. has assembled a strong interdisciplinary mentoring team with expertise in genetics (and pediatric endocrinology (and sex hormone metabolism (and entire mentorship team will meet formally as a group annually to review her progress in her research project and career development. We will also continue informal communication between these annual meetings via email and conference calls, as necessary.

Mentoring & Career Development Plan

During the award period, will have access to my lab space and administrative support. I have 500 sq ft of wet laboratory space for sample processing, DNA extraction, glucose assays and sample storage. In addition, I have 500 sq ft of dry lab space with computer workstations running a variety of statistical and other analytical programs. will continue to receive support from my technical staff, clinical research coordinator and data analyst. I will provide necessary supplemental funding for costs associated with her research project. also provides a number of competitive internal grant opportunities, which will pursue for additional supplemental funding.

will participate in my program's two weekly research meetings, one with the PCOS research group and one with our genetics research group. and (statistical geneticist faculty member), postdoctoral fellows and graduate students participate in these meetings. will continue to present updates on her research progress at frequent intervals. I will also meet with her individually on a weekly basis. At these one-on-one meetings, we review research progress and discuss the preparation of abstracts and manuscripts, as well as presentations of data. I will ensure that she has at least 75% protected time (9 person-months) for research and career development activities. Her , , and , , have also assured me of their ongoing support for her protected time for these activities.

I have worked with to create a career development plan that will enable her to become an independent investigator in clinical and genomic studies of the pathogenesis of PCOS, in particular its developmental origins. She will obtain a Master of Science in Clinical Investigation offered by the that will provide her with formal training in clinical research study design and analysis. will continue to participate in the many additional career development activities offered by , including the monthly *Succeeding with Your K Award* series sponsored directed by . Further, she will continue to attend the monthly New Investigator Career Enhancement seminars offered by the Department of Medicine under my supervision. Finally, will continue to attend and will present her work at our weekly Endocrine Seminar series co-sponsored by the adult and pediatric divisions of endocrinology.

Additional formal course work in statistical genetics will augment the mentoring in genetics she will receive from She will enroll in the Summer Institute in Statistical Genetics offered by the in July 2017 as well as in the Short Course on Statistical Genetics & Genomics offered by the . will continue to attend and present her work at the annual meetings of the Endocrine Society and the Pediatric Endocrine Society. She will also attend the annual meeting of the American Society of Human Genetics to increase her exposure to the latest developments in statistical genetics.

Publication Plan & Progression Towards Independence

It is my expectation that will continue to submit at least two original scientific reports as well as one or more scientific abstracts for presentation at national meetings annually. During her third year as a K23 awardee, I expect that will submit an independent R01 proposal. She will "workshop" this proposal in the grant writing working group directed by . She will also take formal courses on mentoring offered by to prepare her to mentor her own trainees. I fully expect that will successfully garner independent R01 support by the end of her K23 award.

In closing, it has been a great pleasure acting as primary mentor. Her accomplishments to date are impressive. I am very enthusiastic to continue to support her in this next phase of her career development. Following completion of her K23 award, I have every confidence that will be a successful independent physician-scientist who will make high impact contributions to her field throughout her career.

Sincerely,

February 1, 2016

Re: K23 proposal, *A Prospective Study of Biochemical and Genetic Predictors of PCOS in High Risk Early Postmenarchal Girls*

Dear Review Committee:

I am delighted to write this letter to indicate my support and mentorship plan for proposed K23 career development award entitled *A Prospective Study of Biochemical and Genetic Predictors of PCOS in High Risk Early Postmenarchal Girls*. first approached me to be a part of her mentorship team for her K12 BIRCWH award two years ago. Since that time, I have met with on numerous occasions to discuss my work investigating reproductive physiology and pathology in childhood and adolescence. I have provided feedback regarding her work in this area, and she has frequently consulted with me with questions regarding clinical protocols she has developed for her investigations of the reproductive phenotypes of PCOS daughters and obese girls. I am very happy to continue to aid in these ways in her next career step through her K23 proposal.

I am currently at My background has been in studies of puberty and sex development during childhood and adolescence, with a special interest in PCOS. I had continuous NIH grant support for my research in this area from 1971-2009, including the NICHD grant , for 28 consecutive years. I have made mentorship of junior investigators a priority during this phase of my career. I have a long-standing history of successful mentorship in the past, having been primary mentor of over a dozen MD postdoctoral trainees and a mentor for several MD, PhD, and one DVM, PhD junior faculty. Many of my mentees have gone on to successful academic careers and one has had consistent independent funding in PCOS research.

During her time as a K23 awardee, I will continue to meet with quarterly and as otherwise needed for discussions regarding her clinical protocol, feedback regarding manuscript preparation, and career development discussions. As a *pediatric* physician-scientist with a wealth of clinical research experience and expertise in PCOS and related hyperandrogenic disorders in childhood, adolescence, and young adulthood, my role continues to be a critical component of her mentorship team. I have helped develop a career development plan which will provide her with the formal instruction and scientific exposure necessary to prepare her for her independent career in clinical research. is an outstanding candidate for this award. I have been very impressed with work to date, am pleased that she is addressing important gaps in knowledge about developmental aspects of PCOS, and have the highest confidence that she has the qualities necessary to succeed as an independent physician-scientist.

Sincerely,

January 25, 2016
Re: K23 proposal, *A Prospective Study of Biochemical and Genetic Predictors of PCOS in High Risk Early Postmenarchal Girls*

Dear Review Committee:

I am delighted to write this letter indicating my willingness to serve as a mentor for proposed K23 career development award (*A Prospective Study of Biochemical and Genetic Predictors of PCOS in High Risk Early Postmenarchal Girls)*. I have worked informally with over the past two years through our PCOS genetics group at During these recent years, I have helped begin to explore the genetics of PCOS, though approaches focused on identification of both common and rare genetic variants which may play a role in PCOS pathogenesis. I was thrilled that wanted to expand her experience in the collection and interpretation of genetic data as a component of her K23 project.

My background has been in genetics of complex diseases, with a special interest in PCOS. I am trained in Molecular Biology and Genetics and have 20 years experience in applying statistical genetics methods to the identification of genes for complex traits and 17 years studying PCOS. These studies have resulted in the publication of 52 peer reviewed publications with over 2500 citations. Our research uses state-of-the-art genetic technology to identify POCS susceptibility loci. I was a co-investigator in our group's recent study and am an active member of the which is completing the . I am also a co-investigator on our funded by the National Institute of Child Health and Human Development in which I am investigating epigenetic mechanisms of PCOS. I have had success as a mentor in the past, having mentored 12 MD and PhD junior faculty, including those supported by K23 and K08 awards. I have also provided career development mentorship to a number of junior faculty members including through my role as ( ) of our NICHD-funded BIRCWH ( ) program. These experiences qualify me as an ideal genetics mentor for

During her time as a K23 awardee, will have full access to my wet laboratory space, which is adjacent to wet laboratory. In my lab, will have access to all equipment needed for molecular genetic and DNA polymorphism analysis. We also have access to a 3100 ABI sequencer for DNA sequencing and STRP genotyping and a Roche Light Cycler 480II both of which are common equipment for the Division of Endocrinology and a 7900HT ABI DNA analyzer located in our sequencing core.

I will continue to meet with weekly during our PCOS genetics group standing meetings, and one-on-one as needed to discuss her progress on the genetics aims of her K23 project. I have helped develop a career development plan which includes the formal instruction necessary to expand her knowledge of the genetics of complex diseases. I am confident that has the intelligence, drive, and work ethic necessary to be a successful, independent physician-scientist and am thrilled to help her achieve that goal.

Sincerely,

January 29, 2016

Re: K23 submission ***A Prospective Study of Biochemical and Genetic Predictors of PCOS in High Risk Early Postmenarchal Girls***

Dear

We are pleased to accommodate your MRI studies for ovarian morphology and MRS measurement of intrahepatic and intramyocellular/extramyocellular fat, which you will be performing in peripubertal PCOS daughters, obese girls, and control girls. These studies will be performed on our 3 Telsa Siemens scanner. No sedation or contrast agents will be required for these studies. Through our long collaboration we have scanned a number of these kids without any issues or cancellations because of limitation on the magnet bore size. I expect that to continue with this project as well.

We have a great deal of experience performing scans in this age group. We have developed a number of tools, comfort devices, and procedures to make the setup easy and reproducible for the large number of functional imaging studies we run in this age range. We can easily adapt these to facilitate your study and provide you with the high quality data possible. We perform quality assurance measures every day to ensure the MRI scanners are running at their best. Unlike most imaging centers, we utilize a high fidelity two-way communication system. This makes the kids feel better and provides a better way to communicate. We can also provide music and videos to make them feel more comfortable during the study.

We look forward to continuing our long-standing collaboration in your studies of PCOS daughters.

Best of luck with your proposal.

INSTITUTIONAL ENVIRONMENT

The institutional environment at of and offers an outstanding opportunity to achieve her career goals, complete her research strategy, and transition to research independence.

Division of Pediatric Endocrinology & Division of Endocrinology, Metabolism & Molecular Medicine

will take advantage of the close collaboration between the Divisions of Pediatric Endocrinology and Endocrinology, Metabolism, & Molecular Medicine to engage with a number of investigators with complementary research interests. The Division of Pediatric Endocrinology, headed by **,** has a strong history of high quality research in pediatric metabolic disease. is a senior investigator interested in type 2 diabetes in youth, insulin resistance, and the metabolic syndrome. is site PI for the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Follow-up study, which aims to investigate the association of mild gestational hyperglycemia on metabolic outcomes in offspring. is also the site Principle Investigator for several studies sponsored by TrialNet, an international consortium which explores avenues to prevent type 1 diabetes. is a former BIRCWH K12 scholar interested in the effect of the intrauterine environment on obesity risk in children. She is a co-Investigator for the HAPO Follow-up study at .

The Division of Endocrinology, Metabolism & Molecular Medicine at is headed by **.** Research in the Division is supported by over $9 million in annual funding. Areas of interest complementary to work include: maternal fetal health complications of pregnancy **(** **)**, genetic factors in gestational diabetes mellitus **(** **)**, and the circadian basis of obesity, pancreatic β-cell function, and metabolic epigenetics **(** **)**. regularly interacts with investigators from the Division of Endocrinology through the weekly Endocrine Seminar Series and other meetings.

Research Institute/

is also a center of excellence in the basic science of female reproduction. , former of the Endocrine Society, heads the and . These collaborative efforts seek to elucidate the biological and molecular mechanisms which regulate the development of the ovarian follicle in order to translate this knowledge into improved clinical techniques for fertility preservation.

Research Institute

Developed through a generous gift to of in 2014, the comprises the research resources at . The Clinical Research Unit (CRU) at is a dedicated space for investigators to engage in pediatric clinical research within an optimal environment that offers a flexible infrastructure and highly trained staff, thereby assuring excellence in the conduct of clinical research. The Research Institute also offers the Biostatistics Research Core (BRC), a core facility of the which is available to assist investigators with research projects from inception through final analysis.

Clinical and Translational Sciences Institute ( )

provides a broad range of coursework, scientific seminars, and career development activities relevant to career development. The , funded by a $30 million award from the National Center for Research Resources ( ) and directed by , is a tremendous resource that will use throughout this award. These resources include the Master of Science in Clinical Investigation Program, career development and grant writing workshops led by , and numerous conferences and meetings through which will be able to interact with both senior and junior faculty across the institution.

This combination of support from multiple areas of and will provide with a wealth of relevant expertise in clinical research and genetic analyses which will aid in her progression toward R01 funding. is therefore an ideal environment for career development.

February 9, 2016

Re:

Dear NIH Review Committee:

I am writing to express our department's strongest possible support for application for the NIH K23 Career Development Award entitled, "*Prospective Study of Biochemical and Genetic Predictors of PCOS in High Risk Early Postmenarchal Girls*." is excellently trained with a strong track record of success in clinical research, making her an ideal candidate for this award.

After completing her pediatrics residency as well as a chief resident year at in joined our institution in July of 2010 for her fellowship in Pediatric Endocrinology. excelled in both her clinical work and especially in her clinical research efforts under the direction of her mentor, at Early in her fellowship, completed a clinical study investigating the metabolic and reproductive phenotype of daughters of women with PCOS during early puberty. She found that these daughters have evidence for hyperandrogenemia and pancreatic β-cell dysfunction even at this early developmental stage. presented these findings during an oral session at the 94th Annual Meeting of the Endocrine Society and was first author on the manuscript published in the *and* in October 2014. followed up on these findings by investigating alterations in androgen production and/or metabolism in PCOS daughters during early childhood, through measurement of steroid hormone metabolites. She found that the PCOS daughters had evidence for increased 5α-reductase activity, intriguingly a feature also seen in women with PCOS. She presented these findings during an oral session at the 95th Annual Meeting of the Endocrine Society and authored the manuscript currently in revision for the . This early work has set the scientific foundation for this innovative proposal that aims to identify biomarkers much earlier in girls' development in order to predict—and therefore ultimately prevent—the development of PCOS and consequent morbidity and reduced quality of life.

We were thrilled to have join our faculty as an Instructor of Pediatrics in September 2013. In July 2014, she was selected as a K12 scholar through our institutional Building Interdisciplinary Careers in Women's Health (BIRCWH) program funded through NICHD. She was promoted to at the in September of 2015.

As , I commit that will continue to have 75% of her time protected to continue her research activities. Additionally, both her , , and I have adjusted her clinical schedule as needed to facilitate all her career development activities and course work offered through our CTSA sponsored, programs and evolving faculty development programs being established at including a "K to R Bootcamp." We are highly dedicated to supporting development to become an independent and successful physician-scientist, and feel she is well on her way to achieving this goal. A K23 award would provide the final step necessary towards her goal of independence.

In summary, has comprised a highly innovative and important proposal addressing the significant challenge of PCOS and is an excellent candidate for this award. She has my most enthusiastic recommendation and strong support to ensure she achieves her goal of establishing a funded, independent research program. Please do not hesitate to contact me if I can be of further assistance.

1. SPECIFIC AIMS

Polycystic ovary syndrome (PCOS) is a common disorder associated with major adverse health outcomes including subfertility and increased risk for type 2 diabetes (1). The 2015 Pediatric Endocrine Society consensus statement recommended that the diagnosis of PCOS not be made until the otherwise diagnostic features of hyperandrogenemia (HA) and oligomenorrhea persist for 2 years post-menarche (2). Indeed, there has been significant controversy regarding the diagnosis of PCOS during adolescence due to uncertainty regarding the persistence of oligomenorrhea and challenges in accurate measurement of androgens during this developmental stage (3-6). These factors prevent the early diagnosis of PCOS and often delay treatment or prevention approaches in affected girls. Limited but intriguing evidence suggests early interventions such as metformin may be effective in preventing progression to PCOS in girls at high risk (7, 8). Therefore, there is a critical need for identification of early markers of PCOS in girls at risk.

PCOS is a complex genetic trait which arises from a combination of genetic risk and environmental factors such as obesity. We have found early reproductive and metabolic phenotypes characteristic of PCOS in peripubertal daughters of affected women (PCOS-d), including HA and pancreatic β-cell dysfunction, suggesting the pathogenesis of PCOS in these girls may begin prior to puberty (9). HA is also present in obese peripubertal girls (OB-g), which some investigators suggest may be an early sign of PCOS in this risk group (10, 11). However, there have been no longitudinal studies of hyperandrogenic PCOS-d or OB-g beyond menarche to determine if early HA persists as a marker for PCOS in these girls.

My overarching hypothesis is that androgen exposure in the setting of genetic susceptibility programs PCOS-d during critical development periods to produce the phenotypic features of PCOS, including HA. In contrast, the HA observed in OB-g arises from distinct mechanisms. This proposal seeks to: 1) delineate the early postmenarchal reproductive and metabolic phenotypes of PCOS-d and OB-g, 2) determine whether these phenotypes are reliable evidence for PCOS through longitudinal follow up, and 3) evaluate a genetic risk score (GRS) for PCOS in adolescent girls. This study will validate biochemical and genetic markers of PCOS, advancing the field towards development of early treatment and prevention approaches in affected girls. My specific aims are as follows:

Aim 1 – To test the hypothesis that metabolic and reproductive phenotypes differ in early adolescent postmenarchal PCOS-d and OB-g. Early postmenarchal PCOS-d will be compared to control girls (CON) of comparable body mass index (BMI) and OB-g.

1a – Early adolescent PCOS-d will have ovarian HA and increased antral follicle count, which OB-g will lack. Ovarian HA will be assessed by 17-hydroxyprogesterone response to GnRH agonist stimulation and serum testosterone levels after dexamethasone suppression. Ovarian morphology will be assessed by MRI.

1b – Early adolescent postmenarchal PCOS-d will have evidence for pancreatic β-cell dysfunction, a metabolic feature of PCOS, which OB-g will lack. Insulin and glucose responses will be measured during an oral glucose tolerance test.

Aim 2 – To test the hypothesis that early postmenarchal PCOS-d with ovarian HA will fulfill diagnostic criteria for PCOS at postmenarchal age three years, while hyperandrogenic OB-g will not. The PCOS-d, OB-g, and CON will be recalled at three years post-menarche. Hyperandrogenic PCOS-d will meet NIH criteria for PCOS, while hyperandrogenic OB-g will lack oligo/anovulation, a necessary NIH criterion for PCOS.

Aim 3 – To test the hypothesis that a PCOS GRS will be associated with PCOS diagnosis at three years post-menarche. PCOS-associated GWAS single nucleotide polymorphisms (SNPs) will be genotyped in the PCOS-d, OB-g, and CON at three years post-menarche in order to calculate a PCOS GRS. GRS will be compared between girls meeting diagnostic criteria for PCOS and girls without features of PCOS.

It is my long term goal to study the developmental origins of PCOS in order to translate findings into improved prevention and treatment approaches. The proposed research will have a sustained and lasting impact on the field as it will identify early clinical and genetic markers of PCOS in at-risk groups. Completion of this study will provide me with invaluable training in execution of physiologic protocols and statistical genetics, and will position me to successfully apply for independent funding.

2. RESEARCH STRATEGY

2.1 Significance.

2.1.1. PCOS is a Public Health Concern. Polycystic ovary syndrome (PCOS) is a common endocrine disorder with a prevalence of ~7% in reproductive-age women worldwide (1). This disorder is associated with poor reproductive outcomes, such as hirsutism, infertility, gestational diabetes and other pregnancy complications (1). PCOS is also associated with poor metabolic outcomes, including insulin resistance and increased risk for type 2 diabetes (T2D), which begin during adolescence (12, 13). Accordingly, PCOS represents an important public health risk to adolescent girls.

2.1.2. Challenges in Diagnosis during Adolescence. The diagnosis of PCOS in adolescence has been an area of controversy (14, 15), as some features of the syndrome, such as irregular menses and an increase in ovarian follicles, may be normal findings during puberty (5, 6, 16). Normal adolescent ovaries have a multifollicular appearance (2), which is difficult to differentiate from polycystic ovarian morphology (PCOM) by transabdominal ultrasound. Therefore, the 2015 Pediatric Endocrine Society consensus statement recommended against using PCOM as a diagnostic criterion during adolescence; rather, persistent hyperandrogenemia (HA) and oligo/anovulation past postmenarchal age 2 years were recommended as definitive PCOS criteria. (2). The challenges involved in making a definitive earlier diagnosis of PCOS have stalled efforts toward development of early treatment and/or prevention strategies.

2.1.3. Early Phenotypes in PCOS Daughters and Obese Girls. Because PCOS is highly heritable (17), daughters of affected women (PCOS-d) are likely at increased risk. Indeed, PCOS-d have some reproductive features of the syndrome early in development, including increased testosterone (T) and anti-Mullerian hormone (AMH) levels by the time of peripuberty (9, 18, 19). The increased T levels indicate that PCOS-d have HA, a diagnostic criterion for PCOS, prior to completion of puberty (9, 19). The increased AMH suggests PCOS-d also have alterations in ovarian follicular development (18, 20, 21).

We have also found a distinct early metabolic phenotype in peripubertal PCOS-d, characterized by decreased disposition index (DI) (9). In the setting of normal β-cell function, as insulin sensitivity decreases, insulin secretion increases in a compensatory manner to maintain a constant hyperbolic relationship (22). This relationship, the product of insulin secretion and insulin sensitivity, is known as DI (22). Individuals with DI below the 50th percentile in the normal population have increased risk for T2D (23). We found significantly decreased DI in peripubertal PCOS-d compared to control girls (CON) (9) at a younger age than most other studies in populations at high risk for T2D (24-26). Therefore, PCOS-d may be among the youngest children identified to be at high risk for T2D.

Elevated total and free T levels are also present in obese girls (OB-g) over the course of the puberty compared to nonobese CON (11, 27). It has been proposed that these hyperandrogenic OB-g are at high risk to develop PCOS (28). However, no prospective studies have been performed to substantiate this hypothesis. It is also unclear if the HA observed in PCOS-d and OB-g result from common mechanisms (21). We have observed differences in the reproductive phenotypes of PCOS-d and OB-g during early puberty. In contrast to PCOS-d, we have found that peripubertal OB-g have *decreased* AMH levels, suggesting that they lack alterations in ovarian follicular development characteristic of PCOS (21). *These distinct reproductive phenotypes may represent the differing effects of PCOS susceptibility genes vs. environmental factors such as obesity on development of the PCOS phenotype.*

2.1.4. Genetics of PCOS. Almost 20 PCOS susceptibility loci have been reproducibly mapped in PCOS cohorts of Han Chinese (29, 30) and of European ancestry (31, 32) diagnosed by Rotterdam and NIH criteria. While these common genetic variants confer modest risk for PCOS, the predictive power of these susceptibility loci may be increased by summing the loci into a genetic risk score (GRS), as investigators have done in other metabolic disorders such as coronary artery disease (33) and ischemic stroke (34). Indeed, a PCOS GRS compiled from susceptibility loci identified in the Han Chinese GWAS (29, 30) was strongly associated with PCOS in a cohort of Korean women (35). Due to ethnic and racial differences in genetic variation, this GRS is unlikely to be predictive in other ethnic populations.

2.2. Innovation. *This proposal's innovation is largely centered in the overarching hypothesis that PCOS is distinct from simple hyperandrogenic obesity*. I aim to identify early clinical evidence for PCOS at an age prior

to postmenarchal year two, the current standard for early diagnosis of PCOS. This innovative approach will establish which early reproductive and metabolic phenotypes are reliably predictive of PCOS. Finally, this proposal seeks to establish a novel PCOS GRS with recently-identified susceptibility loci.

2.3. Approach

2.3.1. Preliminary Data

2.3.1.1. Reproductive Phenotypes in Peripubertal PCOS-d. We investigated reproductive phenotypes in 12 premenarchal PCOS-d, BMI >85th- ≤98th percentile and 10 CON of comparable age, breast TS, and BMI (9). PCOS-d, as compared to CON, had higher total T (14±4 [SD] PCOS-d v 9±8 CON ng/dL, P=0.0012) and bioavailable T (6±3 PCOS-d v 3±4 CON ng/dL, P=0.0007) (9). We observed increased T and bioavailable T levels in PCOS-d at an earlier pubertal stage than was reported in a Chilean cohort of PCOS-d (19). There were no changes in other circulating androgen or in gonadotropin levels so the source of increased T production is unknown. This early increase in glandular steroidogenesis in peripubertal PCOS-d suggests that the reproductive changes of PCOS may begin prior to puberty. We reported these findings in *J Clin Endocrinol Metab* in 2014 (9).

2.3.1.2. Metabolic Phenotypes in Peripubertal PCOS-d. Early studies investigating the metabolic phenotype of PCOS-d used oral glucose tolerance tests (OGTT) (36) or fasting proxies (37) to assess insulin sensitivity. However, these indirect measures (36, 37) are confounded by differences in pancreatic β-cell function, insulin clearance and glucose absorption (38). We performed frequently-sampled IV glucose tolerance tests (FSIGT) for direct measurements of insulin sensitivity and secretion in this cohort of premenarchal PCOS-d and CON, who were studied prospectively for 3 yrs (9). Insulin sensitivity (SI), acute insulin response to glucose (AIRg), and DI were calculated by minimal model analysis (39-41). An OGTT was performed for calculation of oral DI: the product of the acute insulin response to glucose multiplied by a measure of insulin sensitivity (Section 2.8.3., (42)). There was a trend toward decreased SI (P=0.11) in PCOS-d. However, DI was significantly decreased in PCOS-d (2152±1400 PCOS-d v 4026±2249 CON, P=0.01). Oral DI was similarly decreased in the PCOS-d (0.12±0.03 PCOS-d v 0.21±0.12 CON, P=0.02), validating the use of oral DI as a proxy of FSIGT-derived DI. The significant decrease in DI persisted in PCOS-d (P=0.003) during longitudinal follow-up, in the absence of differences in BMI or visceral adiposity between the groups. These findings suggest that β-cell dysfunction, rather than insulin resistance *per se*, is an early defect in glucose homeostasis in PCOS-d. We reported these findings in *J Clin Endocrinol Metab* in 2014 (9).

2.3.1.3. Distinct Reproductive Phenotype in PCOS-d compared to OB-g. We investigated reproductive phenotypes in 40 premenarchal (Breast TS I-III) PCOS-d compared to 25 OB-g and 18 lean control girls (LC) of comparable age (21). PCOS-d and OB-g had similar increases in free T levels compared to LC (Figure 1)(21). Fifty-six percent of the peripubertal (Breast TS I or II) PCOS-d had HA, defined as greater than 2 SD above the mean in the LC (21). This is analogous to the prevalence of HA in adult sisters of women with PCOS, which is ~ 46% (43). In contrast, 82% of the peripubertal OB-g had elevated free T levels, suggesting that HA is a common feature of obesity in women, rather than an early marker for PCOS (21).

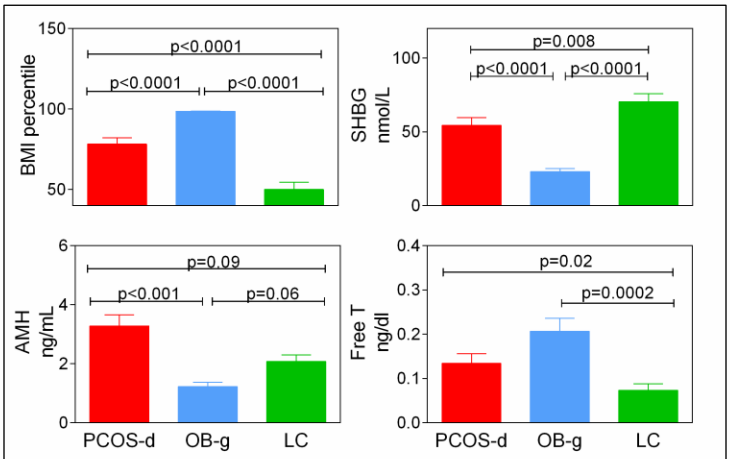

Figure 1. Unique reproductive phenotype in PCOS-d vs. OB-g. Peripubertal PCOS-d (n=40) and OB-g (n=25) had increased free T levels when compared to LC (n=18) of comparable age and breast TS. OB-g had significantly decreased AMH compared to PCOS-d and LC. After correcting for differences in BMI, PCOS-d had significant increases in AMH compared to both OB-g and LC, but levels did not differ in OB-g compared to LC, (ANCOVA P=0.0003, PCOS-d v. OB-g P=0.04, PCOS-d v LC P=0.01, OB-g v. LC P=0.93), suggesting PCOS-d status was the major determinant of increased AMH in PCOS-d.

AMH levels were significantly increased in PCOS-d compared to OB-g (Figure 1)(21). The lower AMH levels in OB-g suggest that they lack an increase in ovarian follicles, which is a key feature of the PCOS phenotype. I presented these findings during an oral session at the 97th Meeting of the Endocrine Society, March 2015 (21), and the manuscript is in preparation.

2.3.1.4. Assessment of Ovarian Morphology by MRI in Premenarchal Girls. We performed magnetic resonance imaging (MRI) scans on 3.0 Telsa Siemens scanners for assessment of ovarian morphology in premenarchal girls (Figure 2), demonstrating that measurement of ovarian size and antral follicle count (AFC) by MRI is feasible during this early developmental stage and is superior to transabdominal ultrasound.

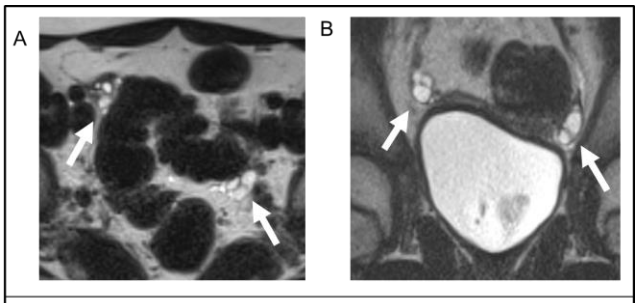

Figure 2: MRI of Premenarchal Ovarian Morphology. Axial (Panel A) and Coronal (Panel B) images of ovarian morphology in premenarchal girls. Arrows denote right and left ovaries.

2.3.1.5. PCOS Meta-Analysis. We are collaborating with investigators in the PCOS Consortium to complete a Meta-Analysis of PCOS susceptibility loci in 4890 cases and 20,405 controls of European ancestry. All PCOS cases fulfilled either NIH or Rotterdam diagnostic criteria for PCOS. Analysis models were adjusted for age and body mass index (BMI). Preliminary analysis has identified 15 PCOS susceptibility loci meeting genomewide significance (Table 1). These SNPs will be used in the PCOS GRS. Some of the SNPs have been significantly associated with AMH levels in an epidemiological cohort of adolescent girls (31), suggesting they are predictive of one early feature of the PCOS reproductive phenotype.

Table 1. PCOS Meta-Analysis Significant Loci: SNPs for GRS

Chr	rsID	Effect Allele Frequency	OR	OR 95%CI	Gene	p-value	Effect Allele
2	rs7563201	0.4507	0.9	(0.87-0.93)	THADA	3.68E-10	A
2	rs2178575	0.1512	1.18	(1.13-1.23)	ERRB4	3.34E-14	T
5	rs13164856	0.7291	1.13	(1.09-1.18)	IRF1 / RAD50	1.45E-10	T
8	rs804279	0.2616	1.14	(1.10-1.18)	GATA4	3.76E-12	T
9	rs10739076	0.3078	1.12	(1.07-1.16)	PLGRKT	2.51E-08	A
9	rs7864171	0.4284	0.91	(0.88-0.94)	FANCC	2.95E-08	A
9	rs9696009	0.0679	1.22	(1.15-1.30)	DENND1A	7.96E-11	A
11	rs11031005	0.8537	0.85	(0.82-0.89)	ARL14EP / FSHB	8.66E-13	T
11	rs11225154	0.0941	1.2	(1.13-1.26)	YAP1	5.44E-11	A
11	rs1784692	0.8237	1.15	(1.10-1.14)	ZBTB16	1.88E-10	A
12	rs2271194	0.416	1.1	(1.07-1.14)	ERRB3 / RAB5B	4.57E-09	T
12	rs1795379	0.2398	0.89	(0.86-0.92	KRR1	1.81E-09	T
16	rs8043701	0.815	0.88	(0.85-0.92)	TOX3	9.61E-10	A
20	rs853854	0.4989	0.91	(0.88-0.94)	MAPRE1	2.36E-09	A
X	rs151212108	0.0765	1.72	(1.43-2.07)	ARSD	8.35E-09	A

2.3.2. Study Design

I will study the reproductive and metabolic phenotypes of 36 PCOS-d, 36 CON with no known family history of PCOS, matched for BMI with the PCOS-d, and 36 OB-g (BMI ≥95th percentile) with no known family history of PCOS. All girls will be less than 2 years post-menarche at the time of baseline phenotyping, prior to the age at which definitive diagnosis of PCOS can be made. All girls will be Caucasian, of European ancestry, due to ethnic differences in genetic variation.

An OGTT will be performed for calculation of oral DI (Figure 3). Ovarian androgen production and gonadotropin responses will be assessed with a GnRHa stimulation test (19, 44) (Figure 3). A low dose short dexamethasone androgen-suppression test (SDAST) will also be performed for measurement of ovarian androgen production (45). MRI will be performed for assessment of ovarian size and follicle number (46).

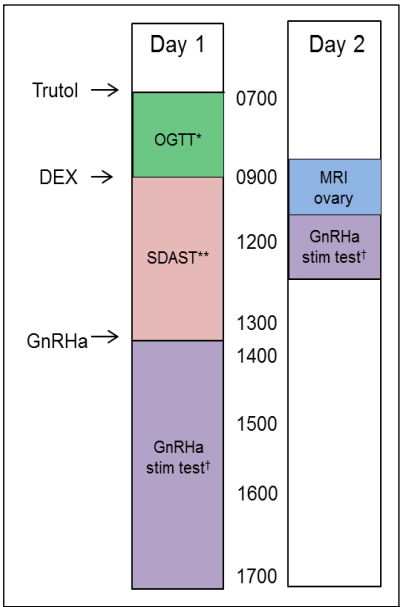

Figure 3 – Baseline Phenotyping protocol.

This cohort of PCOS-d, OB-g, and CON will be recalled after 3 years post-menarche. Serum progesterone will be measured weekly for one month for determination of ovulation status (47). The SDAST and GnRHa tests will be repeated to evaluate for persistent functional ovarian HA (FOH) (45, 48) and menstrual history will be obtained. Girls with persistent HA and evidence for oligo/anovulation will be diagnosed with PCOS (1). The PCOS susceptibility loci from the PCOS Meta-Analysis (Table 1) will be genotyped in the cohort of PCOS-d, OB-g, and CON at the time of longitudinal follow up. The GRS will be evaluated for association with PCOS diagnosis.

2.3.3. Aim 1 – To test the hypothesis that metabolic and reproductive phenotypes differ in early adolescent postmenarchal PCOS-d and OB-g.

2.3.3.1. Aim 1a – Early adolescent PCOS-d will have ovarian HA and increased ovarian size and antral follicle count (AFC), which OB-g will lack.

2.3.3.1.1 Rationale. Our preliminary studies suggest that premenarchal PCOS-d and OB-g have distinct reproductive phenotypes characterized by similarly increased free T levels in both groups compared to LC, but with increased AMH levels in PCOS-d compared to OB-g (Section 2.3.1.3., (21)). The glandular source for the increased free T in PCOS-d and OB-g is unknown. The adrenal glands (49) and ovaries (50, 51) are possible sources for excess androgen production. FOH is a consistent reproductive feature in PCOS, and 20% of women with PCOS also have evidence for adrenal HA (52). Indeed, early FOH was persistent and reliably predictive of PCOS diagnosis in a small longitudinal cohort of adolescents with an early diagnosis of PCOS (48).

The source of HA in OB-g may differ from that in PCOS-d. The adrenal glands may be a source of androgen precursors in hyperinsulinemic OB-g, since insulin increases ACTH-stimulated adrenal androgen production (53). Visceral adipose tissue expresses a number of steroidogenic enzymes including 17β-hydroxysteroid dehydrogenase (17βHSD), which mediates the conversion of androstenedione to T (54). Indeed, adipose tissue contributes up to 50% of circulating T in premenopausal women (55, 56). Therefore, adipose tissue is a potential source for increased T in OB-g.

Increased ovarian size has been proposed as a diagnostic criterion for PCOM in adolescence due to difficulty differentiating the typical multifollicular ovarian morphology from PCOM (2). These are distinct variants of ovarian morphology, however, as multifollicular ovaries are characterized by an increased number of follicles distributed throughout the ovary without an increase in stromal tissue (2), while in PCOM, an increased number of small antral follicles are arranged on the periphery of the ovary, with increased central stroma (57). MRI provides sufficient resolution to measure peripheral AFC in adolescent girls (46, 58). One early study reported increased AFC in adolescents with PCOS compared to age-matched controls, suggesting that polycystic ovaries can be distinguished from the typical multifollicular ovarian morphology typical of adolescence (46). MRI provides superior visualization of ovarian morphology compared to transabdominal ultrasound, particularly in obese patients (59).

AMH levels are increased in PCOS-d, and may reflect an increased number of pre-antral follicles in these girls (18, 60). However, we found that premenarchal OB-g had *decreased* AMH levels compared with both PCOS-d and LC ((Section 2.3.1.3., Figure 1 (21)). A recent study using MRI for assessment of ovarian morphology confirmed that AMH levels reflect the number of small and medium follicles in healthy adolescent girls (58). *Therefore, we can determine if differences in AMH levels are reflective of differences in ovarian follicular development in PCOS-d and OB-g*.

2.3.3.1.2. Study Design. A low dose SDAST and a GnRHa stimulation test will be performed (Figure 2). Post-dexamethasone T concentrations and post-GnRHa 17-hydroxyprogesterone (17-OHP) levels will represent FOH (45, 48, 61-63). Baseline AMH (64) will be measured as a serum index of ovarian follicle count (58). MRI will be performed for measurement of ovarian size and AFC (58).

2.3.3.1.3. Anticipated Outcomes. PCOS-d will have increased 17-OHP responses to GnRHa stimulation and increased post-dexamethasone T levels compared to OB-g and CON, indicating FOH. OB-g will lack increased 17-OHP responses to GnRHa and post-dexamethasone T, suggesting a non-ovarian source for HA. PCOS-d will have increased AMH levels, ovarian size, and AFC on ovarian MRI compared with both OB-g and CON, suggestive of altered follicular maturation typical of PCOS.

2.3.3.2. Aim 1b – Early adolescent postmenarchal PCOS-d will have pancreatic β-cell dysfunction, a metabolic feature of PCOS, which OB-g will lack.

2.3.3.2.1. Rationale. Our preliminary studies suggest that β-cell dysfunction, rather than insulin resistance *per se*, is an early defect in glucose homeostasis in PCOS-d (Section 2.3.1.2., (9)). In contrast, insulin resistance resulting in hyperinsulinemia is likely to be the primary metabolic phenotype in hyperandrogenic OB-g. In peripubertal obese girls with HA, T levels correlated with fasting insulin (65). In our previous study of

reproductive phenotypes in premenarchal PCOS-d compared with OB-g (Section 2.3.1.3), fasting insulin levels were significantly elevated in OB-g compared with PCOS-d and LC, suggesting they may have the greatest degree of insulin resistance (21).

In contrast, studies in adult women have shown that PCOS status is more predictive than BMI of pancreatic β-cell dysfunction, indicated by decreased DI (66). Because decreased DI is the best predictor for T2D (23), it is not surprising that PCOS status, rather than BMI, is also more predictive of T2D in these women (67). Based on our preliminary findings in premenarchal PCOS-d (9), these distinct metabolic phenotypes can be observed early in development.

2.3.3.2.2. Study Design. OGTT will be performed in the PCOS-d, OB-g, and CON. Oral DI (42) will be calculated from insulin and glucose levels measured every 30 minutes during the OGTT (Section 2.8.3).

2.3.3.2.3. Anticipated Outcomes. PCOS-d will have significantly decreased oral DI compared with OB-g and CON, suggestive of pancreatic β-cell dysfunction (42) and increased risk for T2D (23). OB-g will have decreased insulin sensitivity compared to PCOS-d and CON, a difference which will be largely driven by differences in BMI (68).

Aim 2 – To test the hypothesis that PCOS-d with ovarian HA will fulfill diagnostic criteria for PCOS at postmenarchal age 3 years, while hyperandrogenic OB-g will fail to meet these criteria.

2.3.4.1. Rationale. In postmenarchal girls with early diagnosis of PCOS, early FOH is reliable indicator of persistence of PCOS (48). One small prospective study of 8 girls with early diagnosis of PCOS during early adolescence found that FOH at diagnosis persisted and predicted diagnosis of PCOS at recall an average of 8 years later in all girls studied (48).

There have been no longitudinal studies to determine if those peripubertal OB-g and/or PCOS-d with HA ultimately meet criteria for PCOS following menarche. These studies are a necessary and critical step towards the development of early treatment and prevention strategies in girls at risk.

2.3.4.2. Study Design. The PCOS-d, OB-g, and CON who completed the baseline reproductive and metabolic phenotyping will be recalled at postmenarchal age 3 years. I assume that 20% of our original cohort will be lost to follow up. Serum progesterone will be measured weekly for one month; levels over 5 ng/mL will confirm ovulation (47). Reproductive hormones including SHBG, AMH, DHEAS, and T will be measured. Fasting glucose, insulin, and adiponectin will be measured as markers of insulin sensitivity. A GnRHa and SDAST will be performed to test for FOH (Section 2.8.1. and 2.8.2. (45, 48)). Participating girls will keep a menstrual diary for ascertainment of menstrual history. Girls with both HA and oligo/amenorrhea will be characterized as confirmed PCOS cases (Table 2).

Table 2. Aim 2 Endpoints

PCOS	**1) Persistent HA: total or free T greater than 2SD above the mean in CON** **2) Oligo/anovulation: menstrual intervals <20d or >45d (2)**
HA, non-PCOS	**1) Persistent HA: total or free T greater than 2SD above the mean in CON** **2) Regular menses: menstrual intervals between 21-44 days (2)**
Normal	**1) Normal androgens: total or free T within 2SD of the mean in CON** **2) Regular menses: menstrual intervals between 21-44 days (2)**

2.3.4.3. Anticipated Outcomes. PCOS-d with FOH at baseline will have persistent FOH and fulfill NIH criteria for PCOS at postmenarchal age 3 years. Hyperandrogenic OB-g will have persistent HA but regular menses and lack FOH at postmenarchal age 3 years, suggesting the mechanism for HA in these girls differs from that in PCOS-d.

2.3.5. Aim 3 – To test the hypothesis that a PCOS GRS will be associated with PCOS diagnosis at three years post-menarche.

2.3.5.1. Rationale. While common genetic variants identified through GWAS typically confer only modest increases in disease risk, calculation of GRS improved the predictive value of these variants in diseases such as coronary artery disease (33) and ischemic stroke (34). A PCOS GRS (35) comprised of PCOS susceptibility loci identified in Chinese GWAS studies (29, 30) was significantly associated with PCOS in subjects with scores in the highest GRS quartile compared with those in the lowest quartile (odds ratio 6.28,

p<0.001) (35). PCOS susceptibility loci identified in a GWAS cohort of European ancestry were associated with AMH levels in a large epidemiological cohort of adolescent girls (31), suggesting that these loci may be predictive of features of the PCOS phenotype even during adolescence. However, no previous studies have validated a PCOS GRS with PCOS diagnosis in an adolescent cohort of European ethnicity.

2.3.5.2. Study Design. PCOS-associated SNPs will be genotyped in the cohort of PCOS-d, OB-g, and CON in order to calculate a PCOS GRS. An additive PCOS GRS will be calculated by summing the number of risk alleles for each of the genotyped SNPs. A weighted GRS will be calculated by multiplying the number of risk alleles for each SNP by its estimated effect (beta) obtained from the PCOS Meta-Analysis.

2.3.5.3. Anticipated Outcomes. PCOS GRS will be highest in girls meeting NIH Criteria for PCOS after postmenarchal age 3 years (Table 2).

2.4. Limitations and Alternative Outcomes.

2.4.1. Aim 1. It is possible, although unlikely based on previous studies (9, 19, 21), that reproductive phenotypes will not differ in PCOS-d compared with OB-g. This would suggest that these distinct groups share common mechanisms for development of PCOS. It is possible there will be no difference in oral DI between PCOS-d and OB-g. This would suggest PCOS-d and OB-g have similar risk for T2D (23). This would be a valuable finding as establishing degrees of risk in these two potentially at-risk groups is critical in order to focus early treatment and prevention strategies for metabolic disease.

2.4.2. Aim 2. It is possible that there will be no difference in the prevalence of PCOS between hyperandrogenic PCOS-d and OB-g at postmenarchal age 3 years. This would be a valuable finding as it would suggest that early HA predicts PCOS with equal accuracy in PCOS-d and OB-g.

2.4.3. Aim 3. It is possible that there will be no difference in PCOS GRS between girls meeting diagnostic criteria for PCOS and those not meeting criteria. This would suggest that the selected PCOS susceptibility loci are not predictive PCOS diagnosis during adolescence. PCOS-associated SNPs identified through GWAS studies represent genetic markers for regions of the genome which may include genes important in the pathogenesis of PCOS. An alternative approach would be to genotype those genes which are near these SNP regions and have biologic plausibility for a role in PCOS pathogenesis. However, differentiating pathogenic from benign variants identified in these genes would be difficult without genetic data on other affected and unaffected family members.

2.5. Time Plan

Table 2. Study Timeline	Year 1	Year 2	Year 3	Year 4
Baseline Metabolic and Reproductive Phenotyping: PCOS-d, OB-g, CON				
Longitudinal Follow-up: PCOS-d, OB-g, CON				
Genotyping studies for GRS: PCOS-d, OB-g, CON				

2.6. Power Calculations (PASS 2008 Version 8.0.8, NCSS, LLC, Kaysville Utah). My target sample sizes of 36 girls per group for baseline phenotyping studies and 30 girls per group for longitudinal follow-up and evaluation of GRS were based on the following power calculations:

2.6.1. Aim 1a: GnRHa-stimulated 17-OHP and ovarian AFC. A previous study found increased GnRHa-stimulated 17-OHP levels, suggestive of FOH, in PCOS-d compared with CON aged 11-14 years, Tanner Stage IV-V (19). Based on this data, sample sizes of **26** girls per group would achieve 81% power to detect a statistically significant difference between with the groups with alpha of 0.05.

Ovarian morphology was assessed in adolescents with PCOS and age-matched CON using 1.5 or 3 Telsa MRI scanners with a slice thickness of 6 mm (46). AFC in the PCOS adolescents was increased compared with CON (24.0±8.7 PCOS v 13.9±7.1 CON, P=0.0001) (46). Based on this data, sample sizes of **10** girls per group would achieve 81% power to detect a significant difference between the groups with alpha of 0.05.

2.6.2. Aim 1b: Oral DI. Based on our data on oral DI in peripubertal PCOS-d and CON in our previous study (Section 2.3.1.2., (9)), a sample size of **16** subjects per group would achieve 80% power to detect a significant difference in with alpha of 0.05.

2.6.3. Aim 2: Prevalence of NIH Criteria PCOS in Hyperandrogenic PCOS-d vs. Hyperandrogenic OB-g. Based on our preliminary data on the prevalence of HA in PCOS-d and OB-g (Section 2.3.1.3., (21)), I hypothesize that ~50% of PCOS-d will have HA, defined as baseline free T levels over 2SD above the mean of the CON, compared to ~80% of OB-g. Based on findings in sisters of women with PCOS (43), I suspect that the ~50% of the hyperandrogenic PCOS-d will fulfill diagnostic criteria for PCOS, while the prevalence of PCOS in hyperandrogenic OB-g will be more modestly increased over the population PCOS prevalence, ~10%. Based on these assumptions, the sample size of **30** subjects per group provides 86% power to detect a difference in PCOS prevalence between hyperandrogenic PCOS-d and hyperandrogenic OB-g with an alpha of 0.05.

2.6.4. Aim 3: GRS. I assume the prevalence of PCOS in the PCOS-d will be ~25% based on the prevalence observed in sisters of affected women (43), while the PCOS prevalence in the OB-g will be more modestly increased over the population prevalence at ~10%. Based on the data from the Korean GRS study and these assumed prevalence rates, my sample size of **30** girls per group provides 75% power to detect a significant difference in GRS between the groups with alpha of 0.05.

2.7. Statistical analysis Plan. Three group comparisons between endpoint variables in Aim 1 will be assessed by 1-way ANOVA. In Aim 2, differences in prevalence of NIH criteria PCOS in hyperandrogenic PCOS-d compared to OB-g will be assessed by chi square test. ROC analysis will be performed to determine sensitivity and specificity of early biomarkers from the baseline phenotyping studies (FOH, ovarian size, AFC, oral DI) to predict PCOS status at recall. In Aim 3, differences in genotype frequencies between PCOS cases and unaffected girls (Table 2), using both the additive and weighted GRS, will be assessed by chi square test.

2.8. Methods

2.8.1. GnRHa Stimulation Tests (44, 48). GnRHa, 10 µg/kg SC will be given at time 0. Blood will be drawn at time 0 and every hour for 3 h after GnRHa for LH and FSH. Blood will be drawn at 24 h GnRHa for LH, FSH, estradiol, T and 17-OHP.

2.8.2. SDAST (45). Dexamethasone, 0.25 mg/m^2 orally, will be given at time 0. Blood will be drawn at 4 h for cortisol, DHEA, androstenedione, and T.

2.8.3. OGTT. Oral glucose, 1.75 g/kg to a maximum of 75 g, will be administered at time 0 with blood samples for glucose and insulin drawn every 30 minutes for 180 minutes. Oral DI will be calculated as the product of the acute insulin response to glucose (change in insulin (I) divided by change in glucose (G) from 0 to 30 min: ΔI0–30/ΔG0–30) multiplied by a measure of insulin sensitivity (1/fasting insulin) (42).

2.8.4. MRI ovarian morphology (46). MRI scans will be performed on 3.0 Telsa Siemens scanners. High resolution T2-weighted images of the pelvis will be obtained to evaluate the ovaries in the axial, sagittal, and coronal planes. The use of three-dimensional imaging will allow for 1-2 mm slices of the ovaries bilaterally.

2.8.5. SNP genotyping/calculation of GRS. TaqMan SNP genotyping assays will be used to genotype significant PCOS-associated SNPs from the PCOS Meta-Analysis. Additive and Weighted GRS will be calculated as noted (Section 2.3.5.2).

2.8.6. Assays. T assays will be analyzed in the laboratory of Shalendar Bhasin by LC-MS/MS. The assay has a sensitivity of 1 ng/dL and interassay CV <5% (19, 69). All other steroid assays will be performed at Mayo Clinic Laboratories and have <10% interassay coefficients of variation. Estradiol, androstenedione, DHEA, and 17-OHP will be performed by LC-MS (70). DHEAS will be performed by chemiluminescence on the IMMULITE® 2000 platform (Siemens Diagnostics) (71). Progesterone will be performed by electrochemiluminescence (Roche Cobas) (72). SHBG, serum LH and FSH, AMH, insulin, adiponectin and glucose will be determined as reported (9, 71, 73, 74). Non-SHBG bound T will be calculated (75).

PROTECTION OF HUMAN SUBJECTS

1. Human Subjects Involvement, Characteristics, and Design

1.1. Involvement of human subjects. This application proposes to identify clinical and genetic markers of PCOS in PCOS daughters (PCOS-d), obese girls (OB-g), and control girls (CON). We will perform blood tests and MRI imaging of the ovaries in these three groups to characterize their reproductive and metabolic phenotypes. We will also collect DNA through a blood draw in order to genotype PCOS susceptibility loci. We will follow these girls for 2 years in order to identify which girls meet diagnostic criteria for PCOS after 3 years post-menarche. **This study does not fulfill criteria for a NIH-defined Phase III clinical trial.**

1.2. Characteristics of study population. We plan to perform studies to investigate the metabolic and reproductive phenotypes in 36 PCOS-d, 36 OB-g, and 36 CON. These subjects will be aged 11-14 years, postmenarchal, and in good health. We chose the age range of 11-14 years to characterize these phenotypes early after menarche, before a diagnosis of PCOS can be made using current diagnostic criteria.

1.3. Sampling Plan, recruitment and retention strategies, and inclusion and exclusion criteria.
and have recruited more than 500 families with a PCOS index case and first-degree relatives as well as ~3,000 women with PCOS and ~1,000 reproductively normal control women for their genetic analyses of PCOS. has extensive experience recruiting PCOS-d and CON for other studies. She has recruited ~50 PCOS-d ages 12 years and younger and CON of similar ages. She has recruited PCOS-d by contacting PCOS mothers from PCOS Registry. She has also collaborated with David Ehrmann at and Chris Sipe at Fertility Centers of Illinois (FCI) in order to recruit daughters of their patients with PCOS. She has been successful in recruiting obese girls through collaboration with the Wellness & Weight Management program at

Recruitment strategies will include IRB approved advertising and direct contact with healthcare providers. will post notices regarding this study at IRB-approved recruiting website at Printed advertisements may be sent to health care providers and patient support groups, such as the PCOS Challenge: will also post advertisements for potential study subjects on the websites Craig's List and Backpage. Our group at has had success with this web-based recruitment strategy in the past.

and have extensive experience with the recruitment and retention of girls ages 8-12 years in clinical research protocols. Indeed, they completed a 4-year prospective study of a cohort of PCOS-d and control girls retaining most of this cohort for at least 3 years (1). has used gift cards from common retail stores (i.e. Target stores) to reimburse the girls for time and effort. She plans to continue this method of reimbursement in the same amounts as she has used in previous studies. The amount of reimbursement will depend on the length of the study and is greatest for the phenotyping studies, which involve multiple blood sampling protocols.

All subjects will be aged 11-14 years and in good health with no chronic diseases, including hypertension and diabetes. No subject will be taking any medication known to affect reproductive hormone levels or carbohydrate metabolism for at least one month prior to the study, except for oral contraceptive agents, which will be stopped at least three months prior to the study. In the girls, BMI percentiles will be determined based upon Center for Disease Control normative curves (www.cdc.gov/nchs/data/erratas/growthcherrata.pdf). At enrollment, all girls will be postmenarchal, but less than 2 years post-menarche. OB-g will be defined by a BMI $\geq$ 95th percentile. There will be no BMI criterion for PCOS-d. CON will be of comparable BMI to the PCOS-d. Girls will be excluded from these studies if they develop any significant medical or psychiatric illness.

1.4. Vulnerable Populations. While this study does involve the participation of children, we will not study any fetuses, newborns, pregnant women, prisoners, individuals who are or who become incarcerated during the study, youth in DCFS custody or institutionalized individuals. Subjects will be disqualified from the study if they develop any serious medical or psychiatric illness.

1.5. Assignment to Study Group. Subjects will be assigned to study groups as follows: daughters of women with PCOS will be assigned as a PCOS-d, OB-g will have BMI greater than the 95th percentile and a mother with no history of oligo/amenorrhea or hirsutism, CON will have a mother with no history of oligo/amenorrhea or hirsutism will be matched for BMI with the PCOS-d.

1.6. Collaborating sites. All of the proposed studies will be completed at
There will be no collaborating sites.

2. Sources of Materials

2.1. Research materials. Complete medical history, including quantification of exercise, surgical, reproductive and family history will be obtained by a standard questionnaire in all subjects. Blood for phenotyping studies in PCOS-d, OB-g and CON will be obtained by venipuncture. MRI will be performed for assessment of ovarian morphology. All of these procedures are performed solely for research purposes.

2.2. Data to be collected. Results of questionnaire responses, physical assessments performed by a physician, SNP sequencing studies, assessment of ovarian morphology by MRI, and metabolic and reproductive hormone analyses will be collected.

2.3. Access to identifiable private information. Only study investigators and staff will have access to individually identifiable private information about subjects.

2.4. Data collection, management, and protection. Data collection will occur at

All subjects are assigned a code at recruitment and subjects are subsequently identified only by code when their samples are sent to outside laboratories for analysis. Subjects are identified only by code when data are provided for statistical analysis. The DNA will be de-identified prior to genotyping. The subject's name or initials will never be used in any subsequent reporting of the data.

The study investigators and staff only know the identity of the PCOS-d, OB-g and CON who are studied. Study subject charts will be stored in locked office. Keys for identification of study data will be saved only at central sites in password-protected encrypted files on secure computer networks. De-identified assay result data will be saved in encrypted networks at . The study investigators and staff have completed appropriate human subjects training. All investigator laptops with de-identified study data will be also encrypted.

Data will be entered by and verified by a second person on study staff. Quality control queries for out-of-range and illogical data will be performed regularly. All data will be audited from source documents before data are locked.

3. Potential Risks

3.1. Blood withdrawal. The risks associated with blood withdrawal are bruising, bleeding, and phlebitis at intravenous catheter sites. However, these problems are uncommon.

3.2. Oral glucose tolerance test. The risks associated with this test are the risks of blood withdrawal. Some individuals may experience slight nausea when drinking the glucose solution. There is a slight risk of reactive hypoglycemia with this test. These risks tend to be minor.

3.3. Dexamethasone suppression test. The risks associated with this test are the risks of blood withdrawal. There is also a slight risk for transient hyperglycemia due to dexamethasone, although this is unlikely given the low dose used. There is a very small possibility of an allergic reaction to the dexamethasone.

3.4. GnRH agonist (leuprolide) stimulation test. The risks associated with this test are the risks of blood withdrawal. There is a small possibility of an allergic reaction to the leuprolide.

3.5. MRI ovary. There is a risk of discomfort and/or anxiety associated with spending time in the MRI scanner. If any subject complains of discomfort or anxiety while in the scanner, the MRI study will be terminated. There is no radiation exposure with these studies. Only subjects who can tolerate the MRI without the use of sedation will be studied.

3.6. Loss of privacy. There is potential for loss of privacy.

3.7. Alternative treatments and procedures. There are no alternative treatments or procedure for this study.

4. Adequacy of Protection Against Risks

4.1. Recruitment and informed consent

4.1.1. Plans for recruitment and obtaining informed consent. and have maintained a PCOS Registry including more than 500 families with a PCOS index case and first-degree relatives as well as ~3,000 women with PCOS and ~1,000 reproductively normal control women for their genetic analyses of PCOS.

In addition to recruiting PCOS-d and CON by contacting PCOS and control mothers in PCOS registry, will continue her current collaborations with at and to recruit PCOS-d. She will continue her current collaboration with the Wellness & Weight Management Program at for recruitment of OB-g.

Recruitment strategies will include IRB-approved advertising and direct contact with healthcare providers. will post notices regarding this study on IRB-approved recruiting website at Printed advertisements may be sent to health care providers and patient support groups, such as the PCOS Challenge: will also post advertisements for potential study subjects on the websites Craig's List and Backpage.

Written informed consent will be obtained from the subjects' legal guardians prior to participation in any study activities. In addition, written child assent will be obtained after explaining all study procedures to the child in simple language and ascertaining their understanding of the proposed study procedures.

4.1.2. Circumstances for Informed Consent. There will be no waiver of informed consent. All individuals obtaining informed consent will have appropriate human subjects training and certification. The subjects will be informed of the purpose, duration, specific procedures, risks and benefits of the study by or a study coordinator. They will also be informed of their right to withdraw from the study at any time without prejudicing their future care. They will be informed that their anonymity will be maintained and that they will have the right to ask questions of the Investigators or of a patient care representative. Copies of the written informed consent will be given to the participants.

4.2. Protections Against Risk

4.2.1. Procedures for Protecting Against Risk. Subjects enrolled in the proposed study will be disqualified from the studies if they have or develop any of the following: pregnancy, any general medical or psychiatric illness.

4.2.2. Blood Withdrawal. No more than 2 ml/kg of blood will be drawn in a single day during the study. During any 8-week time interval, the amount of blood withdrawn from any subject will not exceed 3 ml/kg.

4.2.3. Confidentiality. Coding of data will ensure confidentiality. The subject's name or initials will never be used in any subsequent reporting of the data. The study investigators and staff know the identity of the PCOS-d, OB-g, and CON. The study investigators and staff have completed appropriate human subjects training. All subject information is kept in locked offices and in secure computer networks with high security standards

maintained by the Information Technology Department. These measures have been effective at preserving subject confidentiality in our research program.

4.2.4. Vulnerable Populations. No pregnant women, prisoners, incarcerated individuals, human fetuses or neonates will be studied. Individuals who become incarcerated will be excluded from the study. Children of age 11-17 years will be studied. In accordance 45CFR46, Subpart D paragraph 406, this study represents no more than a small increase over minimal risk with no prospect of benefit but with increased knowledge about a disorder or condition. Written assent will be obtained from all child subjects prior to participation in any study activities. DCFS wards will not be studied.

4.2.5. Plan for the management of adverse events. In case of adverse effects to the subjects, acute care will be provided by the subject's primary care physician and/or the local emergency room as needed. Information will be provided upon request to the treating physician by or her designee regarding the study protocol and procedures. Subjects will be disqualified from the study if they develop any major medical or psychiatric illness.

4.2.5. Additional protections for children involved as subjects of research. In accordance 45CFR46, Subpart D paragraph 406, this study represents no more than a small increase over minimal risk with no prospect of benefit but with increased knowledge about a disorder or condition. All studies procedures have been approved by the Institutional Review Board of
Written assent will be obtained from all child subjects prior to participation in any study activities.
and have conducted previous NIH-supported research in girls aged 8-12 years that included similar testing to the proposed clinical protocol (1). Extensive efforts will be made to reduce risk to research subjects, including rigorous measures to ensure confidentiality of genetic data. No more than 2 ml/kg of blood will be drawn in a single day. During any 8-week time interval, the amount of blood withdrawn from any subject will not exceed 3 ml/kg.

5. Potential Benefits of the Proposed Research to Human Subjects and Others

5.1. Potential benefits. PCOS is among the most common disorders of adolescent girls and young women, affecting ~7% of this population. It has substantial reproductive and metabolic morbidities. Male as well as female relatives are also at increased risk for metabolic and reproductive morbidities. It is unlikely that the subjects will personally benefit from this research, although glucose intolerance may be detected by OGTT. Further, the OB-g are at risk for metabolic (2-4) abnormalities and hyperandrogenemia (5-7) associated with increased body weight. Accordingly, they may also benefit by having these early metabolic changes identified. The potential benefits to society from this research are substantial. This research may lead to identification of early clinical and genetic markers of PCOS, knowledge that could be used to develop new therapies that could benefit this large population.

5.2. Risk to anticipated benefit. The risks of this study are modest and are related to blood withdrawal and potential loss of privacy. In accordance 45CFR46 Subpart D paragraph 406, this study represents no more than a small increase over minimal risk. Although the child will likely not benefit personally from participating in this study, society will benefit from the increased knowledge about identifying girls at risk for PCOS. Extensive measures will be taken to reduce these risks. There is the potential that this research will have substantial benefits to society by discovering early clinical and genetic markers of PCOS, which could lead to improved treatment and prevention. The risk:benefit ratio strongly favors conducting this research.

6. Importance of the Knowledge to be Gained

6.1. Knowledge to be gained. The objective of this research is to identify early clinical and genetic markers of PCOS. This study may lead to new methods to predict and treat PCOS and its metabolic complications. Given the high prevalence of PCOS—~7% of premenopausal women, and the fact that PCOS-d are also at risk for reproductive and metabolic abnormalities associated with PCOS, this study has substantial public health importance. Accordingly, the potential benefits from the knowledge to be gained are substantial. The risks of the proposed study are modest and the risk:benefit ratio strongly favors conducting the proposed research.

6.2. Risk in relation to knowledge to be gained. The risks of this study are modest and are related to blood withdrawal and potential loss of privacy. In accordance 45CFR46 Subpart D paragraph 406, this study represents no more than a small increase over minimal risk. The risks of the proposed study are modest and ratio of risk to the importance of knowledge to be gained strongly favors conducting the proposed research.

7. Data and Safety Monitoring Plan

The study is NOT a clinical trial and does not fulfill the criteria for an NIH-defined Phase III clinical trial.

8. Registration on ClinicalTrials.gov

This study is NOT a clinical trial and does not fulfill the criteria for an NIH-defined Phase III clinical trial.

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INCLUSION OF WOMEN AND MINORITIES

Planned distribution of subjects by sex and ethnic groups
All subjects will be female. All subjects will be Caucasian of European origin due to racial and ethnic differences in genetic variation.

Subject selection criteria and rationale for selection
We plan to perform studies to investigate the metabolic and reproductive phenotypes in 36 PCOS-d, 36 OB-g, and 36 CON. These subjects will be aged 11-14 years, postmenarchal, and in good health. We chose the age range of 11-14 year to characterize these phenotypes early after menarche, before a diagnosis of PCOS can be made using current diagnostic criteria. All PCOS susceptibility loci we will investigate in this proposal were originally identified in populations of European origin. Therefore, all subjects studied in this proposal will be Caucasian of European origin due to racial and ethnic differences in genetic variation.

Rationale for exclusion of men
PCOS is a syndrome that affects women. While studies have shown that male relatives of women with PCOS may have some reproductive and metabolic abnormalities, they are not affected by the syndrome itself. Because we seek to identify early clinical and genetic markers of PCOS in girls at risk, men cannot be included in the proposed study.

Outreach programs for recruiting sex/gender and racial/ethnic group members as subjects
has recruited more than 500 families with a PCOS index case and first-degree relatives as well as ~3,000 women with PCOS and ~1,000 reproductively normal control women for her clinical and genetic studies of PCOS. The vast majority of these subjects who participated in earlier genetic studies were Caucasian of European origin.

In addition to recruiting PCOS-d by contacting PCOS mothers in PCOS registry, will continue her current collaborations with at and at to recruit PCOS-d. She will continue her current collaboration with the Wellness & Weight Management Program at for recruitment of OB-g.

Recruitment strategies will include IRB approved advertising and direct contact with healthcare providers. will post notices regarding this study at IRB-approved recruiting website at Printed advertisements may be sent to health care providers and patient support groups, such as the PCOS Challenge: will also post advertisements for potential study subjects on the websites Craig's List and Backpage. She has had success with these recruitment strategies in the past.

OMB Number: 0925-0002

Planned Enrollment Report

Study Title: A Prospective Study of Biochemical and Genetic Predictors of PCOS in High Risk Early Postmenarchal Girls

Domestic/Foreign: Domestic

Comments:

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	**0**
Asian	0	0	0	0	**0**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	0	0	0	0	**0**
White	108	0	0	0	**108**
More than One Race	0	0	0	0	**0**
Total	**108**	**0**	**0**	**0**	**108**

Study 1 of 1

Funding Opportunity Number: PA-14-049. Received Date: 2016-02-12T14:39:00.000-05:00

INCLUSION OF CHILDREN

We plan to enroll girls aged 11-14 years in the proposed study. This age range was established because we aim to identify early clinical and genetic markers of PCOS in girls prior to post-menarchal age 2 years, at an age when a formal diagnosis cannot be made. In addition, we plan to follow these girls until after post-menarchal age 3 years in order to confirm which girls are ultimately be diagnosed with PCOS.

and have extensive experience studying children aged 1-12 yrs. The staff at are specifically trained in the care of children. The Clinical Research Unit at is equipped for studies in children and their staff have considerable experience implementing research protocols in this age group.

RESOURCE SHARING PLAN

The primary method by which data generated from this award will be shared will be through peer-reviewed publication and presentations at scientific meetings. I will also submit data and results to the NIH in the progress reports required under the terms and conditions of this award. Datasets will be made available to outside researchers upon request only after careful review by my mentoring team. No identifiable individual level data will be shared. I will freely share our research protocols with other investigators and/or clinicians and will publish protocols and results so that this research may be replicated or extended by other investigators.

is committed to the open and timely dissemination of research outcomes. Investigators in this proposed program recognize that promising new methods, technologies, data, software programs, and insights may arise during the course of their research. All investigators are aware of and agree to abide by the principles for sharing research resources, as described by NIH in “Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Programs." The data generated in this grant will be presented and published in a timely fashion. All final peer-reviewed manuscripts that arise from this proposal will be submitted to the digital archive PubMed Central.