Federal Partners Follow-Up to the National Institutes of Health Pathways to Prevention Program Polycystic Ovary Syndrome Workshop

Wednesday, May 21, 2014
1:00 – 5:00 p.m.

Meeting Summary and Action Items

Submitted to:

Office of Disease Prevention
Office of the Director
National Institutes of Health
6100 Executive Boulevard, Room 2B03
Bethesda, MD 20892-2082

Submitted by:

IQ Solutions, Inc.
11300 Rockville Pike, Suite 901
Rockville, MD 20852
Phone: 301–984–1471
Fax: 301–984–1473

July 1, 2014

Federal Partners Follow-Up to the
National Institutes of Health Pathways to Prevention Program

Polycystic Ovary Syndrome Workshop

Wednesday, May 21, 2014
1:00 – 5:00 p.m.

Agenda

1:00 p.m.	**Welcome and Introductions** **Overview of the Workshop and Goals for the Day** *Louis DePaolo, Ph.D.*
1:10 p.m.	**Overview of Pathways to Prevention Program** *Paris Watson*
1:25 p.m.	**Discussion of Panel Recommendations, Portfolio Analysis, and Research Gaps and Opportunities** *Esther Eisenberg, M.D., M.P.H.*
1:45 p.m.	**Topic I: Polycystic Ovary Syndrome (PCOS) Diagnostics—Methodology, Imaging/Technology, and Genetics/Genomics** *Discussion Lead – Louis DePaolo, Ph.D.* Group Discussion of Gaps and Opportunities
2:25 p.m.	**Break**
2:40 p.m.	**Topic II: Diagnosis of PCOS in Adolescents** *Discussion Lead – Esther Eisenberg, M.D., M.P.H.* Group Discussion of Gaps and Opportunities
3:20 p.m.	**Topic III: Increasing the Dialogue Between Health Care Providers** *Discussion Lead – Esther Eisenberg, M.D., M.P.H.* Group Discussion of Gaps and Opportunities
4:00 p.m.	**Break**
4:15 p.m.	**Group Discussion of Priorities, Next Steps, and Action Items** *Jessica Wu, Ph.D.*
5:00 p.m.	**Adjourn**

SUMMARY

Welcome and Introductions

Louis DePaolo, Ph.D., of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), outlined the highlights of the December 2012 National Institutes of Health (NIH) Workshop on Polycystic Ovary Syndrome (PCOS), including the three areas the workshop panel focused on:

- Benefits and drawbacks of different diagnostic criteria.
- Causes, predictors, and long-term consequences of PCOS.
- Optimal prevention and treatment strategies.

Dr. DePaolo set forth the goals for this Federal Partners Follow-Up Meeting, which included:

- Building on the workshop's momentum.
- Identifying actionable items from the report (e.g., meetings, Funding Opportunity Announcements [FOA]).
- Closing gaps in research.
- Applying information to prevention strategies.

Overview of Pathways to Prevention Program

Paris Watson, of the NIH Office of Disease Prevention (ODP), described the Pathways to Prevention (P2P) program, including the program's goals, workshop format, panel selection process, timeline, and final report publication. This Federal Partners Follow-Up Meeting is the last step in the official P2P process.

2012 Workshop Panel Recommendations, Portfolio Analysis, and Research Gaps and Opportunities

Esther Eisenberg, M.D., M.P.H., of the NICHD described PCOS as a hormonal disorder that affects roughly 5 million reproductive-aged women in the United States. She outlined the recommendations of the 2012 PCOS Workshop:

- Create a new name to replace the term PCOS.
- Maintain broad inclusionary diagnostic criteria of the 2003 Rotterdam consensus workshop.
- Specifically identify the phenotype:
  - Androgen excess ±
  - Ovulatory dysfunction ±
  - PCO morphology ±.
- Establish normal ranges across the age spectrum and across populations.
- Conduct multi-ethnic cohort studies.
- Study prevalence of abnormal glucose tolerance preconception and determine whether treatment, prior to or early postconception, affects maternal fetal outcomes.
- Establish model systems for translational research.
- Conduct large longitudinal epidemiologic studies of various PCOS phenotypes to determine if PCOS is associated with increased cardiovascular and diabetic complications by phenotype and by treatment.

- Study if PCOS is associated with endometrial, breast, and ovarian cancer, and study optimal prevention, detection, and treatment.
- Identify optimal treatment for common symptoms and for achieving a successful pregnancy.
- Improve public and health care provider awareness and management for women with PCOS.

The PCOS Portfolio Analysis found that there are no large multi-ethnic longitudinal cohort studies and few models of translational research. There is no systematic study of various PCOS phenotypes or systematic study at different reproductive and life stages, and there are no longitudinal studies identifying long-term consequences of PCOS. At present, there are very few studies of optimal therapy for specific symptoms or achieving best pregnancy outcomes. In addition, there are no grants specifically studying communication and/or dissemination of information about PCOS. However, by virtue of scientific presentations and publications—which are outcomes of supported grants—communication and dissemination about PCOS occurs.

Topic I: PCOS Diagnostics: Methodology, Imaging, Genomics

Group Discussion of Gaps and Opportunities

Dr. DePaolo reviewed the issues identified by the panel::

- Assessing Androgen Excess
  - Quantification (assays vs. mass spectrometry)
  - Clinical phenotypic expression
- Assessing Ovulatory Dysfunction
  - Criteria for irregular/absent menstrual cyclicity
  - Criteria for normal menstrual cycles by age and race/ethnicity
- Assessing Polycystic Ovarian/Follicular Morphology
  - Imaging (MRI vs. ultrasound)
  - Criteria for PCOS in normal women by age and race/ethnicity
- Developing Biomarkers/Diagnostic Classifiers
  - Role of genomics/proteomics
  - Disease stratification.

Discussion Summary

<u>Screening Technologies</u>

Participants discussed the increased use of mass spectrometry, which is a more sensitive method of analyzing and diagnosing potential cases of PCOS. The move to a simpler test seems necessary. Challenges for moving to mass spectrometry diagnostic tools include the expense of the instruments and the development of both analysis protocols and gold standard biomarkers.

Ultrasound is another diagnostic tool that can be used more effectively and upgraded. A higher-quality machine would help clinicians see all the follicles. On the other hand, MRI, another imaging tool, has proven impractical because of the expense. Access to higher-technology equipment; however, may be difficult for patients in more remote areas, and transvaginal ultrasound may be inappropriate in adolescents.

What Are the Norms?

The group talked about the need to establish the norms—especially for Anti-Müllerian Hormone (AMH)—for each stage of life, for ethnicities, and for obesity, since these have not been studied systematically.

Risk Assessment

One area that can be improved is assessment for risk of PCOS. Patient interviews about family history and other factors could be useful tools. Future risk assessment might involve Genome-Wide Association Studies and other sophisticated methods that could lead to one or more biomarkers for PCOS. To hone in on biomarkers, there needs to be a gold standard, and the field is not yet at that point.

Action Items – Topic I

- Develop mass spectrometry methods.
  - Is there an NIH role?
  - Could small business/private-sector partnerships help refine the technology?
  - What is the role of states/newborn screening?
  - Do the states have the technology?
- Understand genesis and pathophysiology of PCOS.
- Establish what the "norm" is.
  - How does the field get to a stage where development of biomarkers is possible?
  - Should researchers consider genomic possibilities?

Topic II: Diagnosis of PCOS in Adolescents

Group Discussion of Gaps and Opportunities

Dr. Eisenberg identified the issues that complicate the diagnosis of PCOS in adolescents:

- Specific etiology not known.
- Diagnosis is difficult and nonspecific.
  - Irregular menstrual cycles are common during puberty.
  - High ovarian follicle counts are common.
  - Vaginal ultrasound may not be appropriate. (Should AMH or other biomarkers be considered?)
- Normative data are not available.
  - Study of puberty/children across the nation (SPAN or SCAN) was proposed in 2008.
  - Minimal normative data on normal androgen levels and assays are not geared to low levels in children.

Discussion Summary

What are the norms?

The group discussed the importance of advancing diagnosis in adolescents; if PCOS is not identified in those early years, it is difficult to establish etiology. Researchers need to determine the normal range of androgen levels during puberty.

In clinical practice, if the menstrual cycle has not regulated after 2 years, a full workup could become routine. This is an age when having biomarkers would be useful. If you test

testosterone in a young girl, the normal range could be narrowed because more data would be available. Another indicator might be a higher level of AMH (e.g., triple screen in pregnancy).

Testing

While there is no definitive biomarker for PCOS currently, the precision of mass spectrometry may aid in testing for a biomarker once one is identified. For instance, if low androgen levels are found to be associated with PCOS in young children, and if conventional assays are not geared to detect these levels in that age group, mass spectrometry may be beneficial. Analytical methods such as this could be developed after norms are established.

Again, early identification of PCOS could impact patients' lives as interventions might be provided that prevent hirsutism and other symptoms. If there were a specific biomarker or diagnostic test, the next crucial piece would be finding the best age to screen.

Longitudinal Studies

To capture data on this patient population, some participants suggested there needs to be an effort to retain 18- to 24-year-olds in the health care system, because often they no longer see a pediatrician and they haven't yet chosen a new primary care provider. In fact, it might be beneficial to study adolescents who have had consistent care when they were young and to follow them into adulthood. Both patients and practitioners might respond to this in a positive way.

The investigators for the family studies also looked at insulin resistance, as it relates to PCOS. It might yield interesting results if researchers examined existing data, such as those from family studies, and looked at the AMH levels of brothers of women with PCOS.

Utilizing the existing infrastructure of larger longitudinal studies might be a good way to proceed. For example, a study that is set up to follow mothers and children from pre-gestation through reproductive life up to age 25 might gather usable data. Additionally, if there is a subset of people with fertility problems in one of these large studies, researchers could go back and look at their patient histories and biosamples.

As a model, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is issuing a Request for Applications (RFA) on a living biobank. They have used a specific mechanism to take advantage of some long-range studies. PCOS researchers could follow this model and, without interfering with a major study, take advantage of economies of scale. Crucial questions to ask include: Are there research questions to leverage? Are there biobanks? The Puberty Study at the National Cancer Institute (NCI) consortium has already developed a cohort. Asking these researchers whether they have developed best practices and whether there are items they wish they had collected could inform research on PCOS. In puberty, PCOS is relevant to many different disease processes. Among other things, it will be important to determine the timing at which to collect information, as the age of diagnosis has an impact on girls' lives. In the 2012 NIH PCOS workshop, participants discussed educating young girls about managing PCOS.
A first step may be to identify the birth cohorts that different researchers are following longitudinally, and then determine how to leverage these longitudinal studies (e.g., post-puberty family studies.)

Action Items – Topic II

- Use longitudinal studies to understand etiology and pathogenesis.
  - Surveys
  - Secondary analysis of existing data
  - Family history
  - Leveraging of existing opportunities: for example, National Center for Health Statistics (NCHS), birth cohorts
  - Identification of additional tests and screens for detection at an earlier age and to uncover subclinical disease.
- As a group, work to identify variables that would be useful to move forward data collection, cohort studies, etc. (RFAs, FOAs).
- Define hypotheses.
- Prioritize research gaps.
  - Larger, more definitive studies vs. RO1s (e.g., Study of Women's Health Across the Nation [SWAN], virtual cohorts, consortia).

Topic III: Increasing the Dialogue Between Health Care Providers

Group Discussion of Gaps and Opportunities

Dr. Eisenberg listed issues identified by the panelists in December 2012, including the necessity for assigning a new name to the syndrome.

- Assigning a new name may promote collaboration.
- Different manifestations and issues at different life stages
  - Reproductive issues—irregular menses, infertility
  - Metabolic issues—diabetes, obesity
  - Dermatologic, psychological, sleep, quality of life.
- Optimal therapies for specific issues are unknown.
- Long-term consequences are unknown.
  - Diabetes, cardiovascular disease
  - Cancer-breast, endometrial, ovarian.

Discussion Summary

<u>New Name for PCOS</u>

The participants discussed the importance of a new name for this syndrome. Although the term PCOS is recognizable, the name focuses the attention of clinicians on the ovaries and ovarian cysts. Just as the renaming of severe preeclampsia to Hemolysis, Elevated Liver Enzymes and Low Platelet Count (HELLP) syndrome took the focus away from the seizures, a new name for PCOS could bring attention to other aspects of the condition. The 2012 PCOS Workshop Panel concluded that experts should develop the exact name, although they suggested "metabolic reproductive syndrome" (with the acronym "Mrs.").

A new, more comprehensive name would give clinicians and patients a more accurate vocabulary and a description based on the many manifestations of PCOS. At present, a woman may have irregular cycles, but not know there is a condition that may be responsible for her symptoms. A new name could contribute to better clinician, patient, and public health education.

The new name must convey the message that this syndrome is linked to preventable chronic diseases later in life. This messaging could be disseminated during current public health activities (e.g., home visitations).

If “metabolic” were in the name, it would cast a wider net. A clinician would not talk to a 13-year-old about infertility, but might talk to her about glucose intolerance and weight gain.

The group discussed options for how to implement a name change for PCOS. They agreed that a name change will have to involve a dialogue among stakeholders. This could be accomplished by convening a conference to decide on a uniform name, or by organizing a session within another large, established meeting. Sometimes a name change begins to appear in the literature and evolves organically. But since some patient advocacy groups have the syndrome name on their website and materials, it would be necessary to involve advocates and other stakeholders in decision-making.

Messaging

When a name change is effected, then the change, along with good public health information, must be distributed to the public. The way the messaging is framed is important.

Professional and patient societies could help to spread messages, but NIH communications would play an important role. The NIH could provide materials to stakeholders; therefore, we need to identify whom to seek out with our messaging, and what kinds of information and support the stakeholders are seeking. Professional organizations may be able to provide additional information. The American Society for Reproductive Medicine could be a major partner.

The PCOS Society is another potential partner that focuses on adults more than children. It would be helpful for them to have guidance for different patient populations (e.g., adolescents, women concerned with fertility).

One participant described a young adolescent girl with PCOS who was told she would never have children. She is now married and has two children. Stories like this remind the communities involved that there is a lot of information being circulated, not all of it accurate. If we want research to be taken to the next level, we have to disseminate accurate messages.

The NCI might be a model for NIH Institutes and Centers interested in reaching out to patient communities to become involved in research. NCI’s model is based on the message, “become involved in research and help other patients who may later develop this disease.”

The NICHD has taken steps to include more information about PCOS on its website, including a PCOS fact sheet; however, this factsheet has not been updated since the 2012 workshop.

Messaging should reinforce the need for research, whether it is making use of biorepositories, prevention, diagnosis, or therapies. The messaging can drive the research.

Different Manifestations

Different manifestations of PCOS symptoms and issues at different life stages mean different sets of recommendations. Those with PCOS have depression, anxiety, sleep issues, and quality of life issues, and clinicians do not know what the optimal treatment is, or even who the optimal caregiver is. Adolescents go to pediatric endocrinologists. When they become older, they might see an OB-GYN or a reproductive endocrinologist. Do these practitioners know about treating PCOS? And should the pediatrician be more informed? If

all clinicians were informed, internists, primary care doctors, and others could treat this syndrome, not just one group. Helpful messages need to go to more specialists and to primary care physicians.

Some considerations are: What is the "hook" of having patients tested, engaging preventively? Is it the importance, early on, of maintaining a hormonal balance? Will it center around the psychological issues?

Topic III: Dialogue With Health Care Providers

Action Items

- Change the name of the syndrome.
  - Who is responsible for the name change, and how can NIH stay involved?
    - Hold NIH/Centers for Disease Control and Prevention (CDC)-hosted conference with stakeholders on name change issue.
    - Have sub-meeting at existing conference.
    - Model after Australian effort.
- Develop consistent messaging.
  - Early intervention: benefits across the lifespan
  - Recognition of symptoms
  - Potential comorbidities
  - Testing for PCOS in the presence of symptoms/comorbidities.
- Engage with partners.
  - Professional societies
    - Professional education for health care providers
    - Continuing medical education (CME) modules
  - Patient societies.
- Utilize NIH communications capabilities.
  - NIDDK, National Heart, Lung, and Blood Institute (NHLBI) communications efforts
  - NICHD communications items on web, pamphlet, possible fact sheet
  - CDC preconception web page and other pages linking to NICHD web page
  - Updating NIH messaging based on meeting outcomes.

Other Topics Discussed

Surveys

Biobank Michigan had to have community approval for storing genetic materials. They used two surveys to assess approval. The surveys included simple questions: Do you oppose having your genetic information stored? Do you see the benefit? The surveys also had an educational role. Survey prompts can provide valuable knowledge to people, and it would be good to increase such opportunities wherever possible. If clinicians assess how much women know about their PCOS diagnosis, researchers could implement a public health approach by examining secondary data sources. Developing surveys, validating questions, testing, and conducting cognitive questioning is painstaking, but it can be valuable in gathering information. Surveys can ask, "What providers do you go to?" and help to show gaps from a patient perspective and give insights about how to move forward. Surveys can give a sense of what women already know and of further measures needed to inform physicians and patients to develop a screen or identify a biomarker.

Environment

From the perspective of the National Institute of Environmental Health Sciences, to what extent does environmental exposure play a role in the etiology of the syndrome, and what are the relative windows of susceptibility? How important are exposures *in utero* or very soon after birth? Questions remain about whether women with PCOS are susceptible to elements in the environment. Even if environmental issues are not primary, in terms of prevention, environmental tracking might be worthwhile.

Final Session: Questions and Action Items

Jessica Wu, Ph.D., of the ODP, concluded the workshop by focusing on final questions and action items.

Questions:

- What can the NIH do to close research gaps?
- What specific action items are needed?
- What can NIH Institutes and Centers do to contribute to this effort?

Summary of Action Items

Topic I: PCOS Diagnostics

Action Items

- Develop mass spectrometry methods.
  - Is there an NIH role?
  - Could small business/private-sector partnerships help refine the technology?
  - What is the role of states/newborn screening?
  - Do the states have the technology?
- Understand genesis and pathophysiology of PCOS.
- Establish what the “norm” is.
  - How does the field get to a stage where development of biomarkers is possible?
  - Should researchers consider genomic possibilities?

Topic II: Diagnosis Across the Lifespan/Early Intervention/Prevention/Progression

Action Items

- Use longitudinal studies to understand etiology and pathogenesis.
  - Surveys
  - Secondary analysis of existing data
  - Family history
  - Leveraging of existing opportunities: for example, NCHS, birth cohorts
  - Identification of additional tests and screens for detection at an earlier age and subclinical disease.
- As a group, work to identify variables that would be useful to move forward data collection, cohort studies, etc. (RFAs, FOAs).
- Define hypotheses.
- Prioritize research gaps.
  - Larger, more definitive studies vs. RO1s (e.g., SWAN, virtual cohorts, consortia).

Topic III: Dialogue With Health Care Providers

Action Items

- Change the name of the syndrome.
  - Who is responsible for the name change, and how can NIH stay involved?
    - Hold NIH/CDC-hosted conference with stakeholders on name change.
    - Have sub-meeting at existing conference.
    - Model after Australian effort.
- Develop consistent messaging.
  - Early intervention: benefits across the lifespan
  - Recognition of symptoms
  - Potential comorbidities
  - Testing for PCOS in the presence of symptoms/comorbidities.
- Engage with partners.
  - Professional societies
    - Professional education for health care providers
    - CME modules.
  - Patient societies.
- Utilize NIH communications capabilities.
  - NIDDK, NHLBI communications efforts
  - NICHD communications items on web, pamphlet, update fact sheet
  - CDC preconception web page and other pages linking to NICHD web page
  - Updating NIH messaging based on meeting outcomes.

Participant Roster

Chairperson: **Louis V. DePaolo, Ph.D.**
Branch Chief
Fertility and Infertility Branch
Division of Extramural Research
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health

Patrice Desvigne-Nickens, M.D.
Program Director
Heart Failure and Arrhythmias Branch
Division of Cardiovascular Sciences
National Heart, Lung, and Blood Institute
National Institutes of Health

Caroline Dilworth, Ph.D.
Health Scientist Administrator
Division of Extramural Research and Training
National Institute of Environmental Health Sciences
National Institutes of Health

Esther Eisenberg, M.D., M.P.H.
Director
Reproductive Medicine/Infertility Program
Fertility and Infertility Branch
Division of Extramural Research
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health

Violanda Grigorescu, M.D., M.S.P.H.
Branch Chief
Applied Sciences Branch
Division of Reproductive Health
National Center for Chronic Disease Prevention and Health Promotion
Centers for Disease Control and Prevention

Ellen Leschek, M.D.
Program Director
Division of Diabetes, Endocrinology, and Metabolic Diseases
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health

Barbara Linder, M.D., Ph.D.
Program Director
Division of Diabetes, Endocrinology, and Metabolic Diseases
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health

Joan Davis Nagel, M.D., M.P.H.
Medical Officer
Office of Research on Women's Health
Division of Program Coordination, Planning, and Strategic Initiatives
Office of the Director
National Institutes of Health

Paris Watson
Senior Advisor
Office of Disease Prevention
Division of Program Coordination, Planning, and Strategic Initiatives
Office of the Director
National Institutes of Health

Jessica Wu, Ph.D.
AAAS Science and Technology Policy Fellow
Office of Disease Prevention
Division of Program Coordination, Planning, and Strategic Initiatives
Office of the Director
National Institutes of Health