

To submit or view comments on this white paper, please visit the [comments page](#) for this workshop. Comments will be accepted through June 10, 2011.

Eunice Kennedy Shriver National Institute of
Child Health and Human Development
**Scientific Vision Workshop
on Reproduction**

January 25–26, 2011
Bethesda, Maryland

Workshop White Paper

by Workshop Organizers:
(in alphabetical order, by role)

Linda C. Giudice, M.D., Ph.D. (Co-chair)
University of California, San Francisco

Régine Sitruk-Ware, M.D. (Co-chair)
Population Council

William J. Bremner, M.D., Ph.D.
University of Washington

Paula Hillard, M.D.
Stanford University

I. INTRODUCTION/OBJECTIVES/CROSS CUTTING THEMES

Successful reproduction depends on the normal anatomy and function of the female and male reproductive tracts (and other systems), and includes normal menstrual cyclicity and hypothalamic/pituitary/gonadal function, gamete formation and development, fertilization, embryo development, implantation, placentation, and fetal development, and completion of pregnancy to term. An abnormality in any of these processes, whether intrinsic or due to genetic, environmental, and/or systemic diseases, can have a profound impact on procreation, reproductive health, fertility, pregnancy, and overall health including physical, sexual, and emotional health and well-being. Furthermore, the ability to control fertility through the use of effective contraception is an essential component of preventive health, ideally resulting in planned pregnancies during optimal health. Contraceptive methods, based on a fundamental understanding of the processes of successful reproduction, are not only important for individuals and families, but play an essential part in population dynamics and deserve an important place in the science of reproductive medicine. Together, research in reproductive science and medicine are fundamental underpinnings of the goals of the NICHD in ensuring that every child is wanted and reaches their full potential.

The objectives of the NICHD Reproduction Vision Workshop were to identify visionary scientific opportunities that will impact human reproductive health globally and shape the future scientific agenda in reproductive research for the next decade in the context of big science, team science, advanced technologies, targeted diagnostics and therapeutics, disease biomarkers, clinical and translational science, and specific training of a multidisciplinary workforce to achieve these goals.

To this end, 4 plenary speakers gave visionary lectures on themes of reproductive science and medicine and set the tone for the scientific discussions and brainstorming sessions. In addition, we organized 6 thematic sessions focused on: Pre-/Periconceptual Health and Pregnancy Establishment; Developmental Antecedents of Adult Reproductive Diseases/Disorders; Diagnostics and Treatments for Reproductive Diseases/Disorders; Contraception; Quality of Life improvements; and Reproductive Health as a Window to Overall Health.

Several crosscutting themes emerged in the workshop, including the following:

- Overall health and disease affect reproductive health and disease, and reproductive health and disease affect overall health and disease.
- Advancing fundamental knowledge in reproductive and developmental biology, genetics and reproductive medicine is critically needed. In addition to a focus on untargeted science, it is essential to apply advanced technologies and bioinformatics/systems biology to drive novel diagnostic and molecular targets for therapies and to develop biomarkers for conditions and disorders impacting fertility and fecundity in males and females and pregnancy outcome.
- It is essential to broaden the scope of reproduction research and include evaluating the interaction of genetics, epigenetics, environment, behaviors, and socioeconomic status, and to clarify the distinction between phenotypic variation and disease. These efforts will need to take place with an awareness of diverse and at-risk populations.
- Team science and interdisciplinary research, including the fields of social and environmental science and the humanities beyond bioethics, are needed to advance reproductive and developmental research.
- Knowledge of pre/periconceptual health in females and males, as well as processes leading to pregnancy establishment (e.g., fertilization, placentation, implantation), must be expanded, with the goals of

Views expressed herein are the opinions of the authors and do not necessarily reflect those of the NICHD.

improving pregnancy outcomes and minimizing morbidities in women and children, including developmental abnormalities and disabilities and maximizing subsequent health and well being.

- Reproductive research is the cornerstone of stem cell research, cellular differentiation, organogenesis and tissue repair, and consequently is central to the field of regenerative medicine. It is anticipated to be an important foundation for stem cell-based therapies in the future.
- It is essential to develop and apply new and improved imaging tools, nanotechnology, single cell technologies, and animal models in reproductive research. Further development of advanced technologies and supporting infrastructures, such as high-throughput screening, computer models, disease registries, bioinformatics and systematic bio-banking, will be required to advance reproductive and developmental research.
- Fundamental and applied contraceptive research on both newly developed and existing methods for males and females are necessary to reduce the burden of unintended and unwanted pregnancies. It will be necessary to ensure acceptability and effective use of these products in various settings and populations, and to address behavioral issues related to fertility and contraception use in a variety of settings and populations.
- To reduce the incidence of adult male and female reproductive diseases/disorders, a better understanding of a variety of developmental processes is necessary. These include: early developmental processes in utero, the neonatal period, and in children; normal puberty; menstrual cycle dynamics in female adolescents; and the impact of the environment and altered nutrition/disease on reproductive function (e.g., anorexia nervosa or bulimia and obesity).
- Women with gynecological diseases and reproductive tract disorders may experience quality of life issues, which can be impacted by related co-morbid conditions such as infertility, obesity, metabolic dysfunction, chronic pain and mood disorders. Improving therapies and developing novel approaches to diagnose and manage these interrelated conditions may provide opportunities for quality of life improvements in diverse populations and across the lifespan. Quality of life should be assessed at baseline and throughout all clinical studies.
- Reproductive and sexual health is essential to wellbeing and serves as a window to overall health in males and females; because it impacts other body functions and vice versa, attention to reproductive dysfunction can signal risks for other medical conditions.
- New and novel technologies for information gathering and dissemination are needed to develop a national database of prospectively collected reproductive health data (e.g., an NIH social health network). Additional databases could include a comprehensive atlas of genetic information, a national database of pregnancy outcomes, global population databases, and social networks for physicians.
- New methodologies for mining, analyzing, and validating the data and linking new information technology approaches with health information technology will be required.
- How clinical trials are designed and conducted warrants careful reevaluation.
- Mutual benefits can be leveraged through community participation and engagement in research.

II. SCIENTIFIC OPPORTUNITIES

II.1. PRE/PERI-CONCEPTUAL HEALTH AND PREGNANCY ESTABLISHMENT VISION

Views expressed herein are the opinions of the authors and do not necessarily reflect those of the NICHD.

Introduction: To improve reproductive and overall health, as well as QOL, there is a pressing need to understand the effects of pre/peri-conceptual physical, environmental, and psychological health in females and males on pregnancy establishment and outcome and on normal human development. An overarching goal is to create a structural, molecular, and metabolic atlas of human reproduction and development to underpin evidence-based approaches to clinical care in reproductive medicine.

Guiding principles in creating this Vision include:

- Relevance to human reproduction and development
- Science that elucidates fundamental processes that relate to reproduction across species
- Attention to health disparities
- Attention to the environment as a factor affecting development and reproduction
- Attention to the unique ethical issues surrounding scientific discovery in reproductive medicine.
- Attention to education with regard to the changing landscape of science and technology in the field of reproductive health.

Scientific Opportunities: In 10 years we will have elucidated:

1. Normal and abnormal processes in germline development. Determine genetic vs. environmental effects in development; epigenetics of germline reprogramming; origins of genetic and epigenetic errors; efficient preservation of reproductive potential; effects of systemic disorders (e.g., diabetes, inflammatory disorders, autoimmunity) on reproductive potential; effects of abnormal germline development; pathways responsible for germline senescence; optimal timing for reproduction; utility of preconception genetic testing.

2. Normal and abnormal processes in fertilization and pre-implantation development. Determine molecular mechanisms of fertilization; pre-implantation mechanisms of normal and abnormal development; impacts of emerging ART and infertility treatments; consequences of infertility diagnosis.

3. Pluri-totipotency, embryonic stem cells, and early lineage differentiation. Determine how cell fate is established and maintained; map the pathways of pluripotency and reprogramming; elucidate the relationship between embryonic developmental abnormalities and cell lineage determination; discover how gene-environmental interactions affect cell lineage determination; define how maternal disease affects cell lineage; explore therapeutic uses of stem cells.

4. Mechanisms of normal and abnormal embryo-maternal interactions. Define the molecular mechanisms underpinning embryo-endometrial interactions and timing of synchrony; map the interactions between the maternal and fetal immune systems; define how environmental exposures, hormonal dysregulation, reproductive tract disease, and maternal systemic disease impact pregnancy outcome; determine the impact of abnormal implantation on long-term maternal and child health.

5. Reproductive tract stem/progenitor cells. Identify and characterize reproductive tract stem/progenitor cells and niches; elucidate the roles of stem/progenitor cells in reproductive tract disorders; determine the role of mesenchymal-epithelial and epithelial-mesenchymal transitions in reproductive tract diseases; apply findings of regenerative medicine to reproductive tract diseases or other disorders.

What research tools, methods or approaches should be developed to achieve the anticipated outcomes?

Bioengineering tools to establish in vitro models of the reproductive tract niche; biomarkers for embryo quality, uterine receptivity, reproductive tract disorders, and pregnancy outcomes; non-invasive imaging techniques for pregnancy progression; advanced high throughput -omics technologies for diagnostics, discovery and therapeutics; reliable pre-clinical models, including nonhuman primates; advanced technologies: single cell analysis, imaging, applied nanotechnology, non-invasive cell sensors; mechanisms to capture clinical and tissue

data and biobanking to inform evidence-based practices; support registries of ART/twin offspring and their progeny to detect common traits; medical informatic approaches and electronic medical records for ART/infertility treatments; an atlas of normal and abnormal processes in reproduction and early development to provide insight into human infertility, contraception, and consequential disorders, with the ultimate goal of ensuring that every person is born healthy and wanted.

II.2. CONTRACEPTION

Introduction. Societies in both the developing and developed world suffer from unacceptably high rates of unintended and unwanted pregnancies, despite the availability of safe and effective forms of contraception. Factors that contribute to this problem include misperceptions about safety, knowledge, acceptability of methods, compliance, access and cultural factors. Rapid population growth has significant individual, family, societal and environmental effects and contributes to, among other things, high maternal and infant mortality and morbidity in many developing countries.

Scientific Opportunities: In 10 years we will have:

- 1. *Improved understanding of the risk factors for unintended pregnancy and the social and cultural behaviors that facilitate or detract from the correct and consistent use of contraceptive methods.*** This opportunity will be addressed scientifically by: 1) understanding the impact of unintended pregnancy on the individual, as well as on public health and welfare, 2) identifying the determinants of contraceptive use and non-use, and 3) determining what interventions can facilitate increased contraceptive use and decrease contraceptive failure. These will be facilitated, in part, by developing, 1) universal quantitative measures of unintended pregnancy relevant to public and global health; 2) behavioral-based, bioethically sound interventions that help individuals who wish to avoid pregnancy to use contraception effectively; 3) assessments of individual attitudes and pregnancy desire or ambivalence. It is essential to develop these scientifically sound tools to support rational contraceptive use and policy and to direct present and future contraceptive R&D.
- 2. *Improved existing contraceptive methods.*** This will be addressed scientifically by, 1) understanding why misperceptions of risks/benefits of contraceptive use exist and working to improve safety and acceptability; 2) improving cycle control in users of hormonal contraception; 3) identifying the impact of current methods on women with different medical conditions (e.g., PCOS, obesity, HIV, autoimmune disorders) so that clinicians and users recognize the multiple health benefits of contraception; 4) developing approaches to improve adherence, convenience and access to contraceptives; 5) developing ways to increase the use of long-acting, reversible contraceptives; 6) understanding what non-contraceptive health benefits of contraceptives are valued by users, more effectively communicating those benefits, and developing additional benefits based on end-user desire; 7) developing programs to increase successful contraceptive use in order to achieve actual efficacy. This opportunity will be facilitated by, 1) improving epidemiologic tools and validating surrogate markers that predict clinically important outcomes, 2) developing direct measures of efficacy of dual purpose methods (e.g., HIV prevention), and 3) developing animal models to define non-contraceptive health benefits and risks. These strategies will ensure the most effective use of current contraceptive methods, while new contraceptives are developed.
- 3. *Taken the lead in contraceptive research and development.*** Since the 2004 IOM report, where recommendations were made for initiating discussions with the pharmaceutical industry around the development of new and innovative contraceptive targets based on the rapid expansion of new technologies and the “omics,” the pharmaceutical industry has jettisoned many contraception R&D programs. Prospects of

innovative contraceptives for females and males (both hormonal and non-hormonal) have suffered a serious setback. The committee recognized that the NICHD would now need to take the lead in contraceptive R&D and change the research paradigm in this field.

What research tools, methods or approaches should be developed to achieve the anticipated outcomes?

Key are: 1) recognizing that the fields of infertility and fertility intersect and should be collectively mined for contraceptive R&D; 2) identifying those molecular controls of gametogenesis and fertility that can be applied for contraception; 3) developing innovative strategies to identify selective and druggable targets that will lead to new contraceptive modalities with fewer side-effects and non-contraceptive health benefits. This will be accomplished by establishing new and innovative partnerships among academia, government, industry and foundations and will be facilitated by 1) developing strategies from target discovery to proof-of-concept studies, including new animal models, to engage industry in the development of novel contraceptive methods, 2) utilizing and expanding facilities within NIH, academia and industry to identify and develop new contraceptive compounds against new contraceptive targets, 3) working with industry to develop contraceptive targets and compounds and targets; 4) developing specific and predictable standards/assays for preclinical development and proof-of-concept studies within the NICHD and through extramurally-funded research; 5) exploring innovative delivery systems for contraceptive agents; 6) developing behavioral assessments/indicators that predict acceptability/successful use of new contraceptives.

Successful accomplishment of these objectives will, 1) increase the safety, efficacy and use of existing contraceptives, 2) expand acceptability of and access to contraceptives by the introduction of new methods, 3) move toward the goal of eliminating unintended and unwanted pregnancies and improve maternal and child health

II.3. DEVELOPMENTAL ANTECEDENTS

Introduction: Developmental impacts on later-in-life reproductive and overall physical and psychological health are pivotal to well being and reproductive success. Understanding antecedent influences during development will require longitudinal studies in humans and animal models, distinguishing critical windows of development in males and females, and incorporating in experimental design and subject cohorts influences of race, ethnicity, diet, environmental exposures, and chronic and acute diseases and psychological stress.

Scientific Opportunities: In 10 years we will have:

- 1. Elucidated molecular and integrative physiologic mechanisms linking metabolism and reproductive health and disorders:** e.g., the impact of the epidemics of obesity and diabetes and the role of environmental exposures on reproductive and developmental processes from conception to menopause in human and non-human primates using epi/genomics, metagenomics and other advanced technologies and generation of normative data for co-morbidities.
- 2. Collected transgenerational normative deep phenotypic data on offspring of ART and subfertility patients,** along with appropriate familial controls, resulting in comprehensive characterization of the developmental antecedents of later-in-life disorders in these populations.
- 3. Defined what regulates pubertal onset and progression and consequential later-in-life disorders associated with abnormal adolescent gonadal function (e.g., anovulation), timing, and duration.**

4. Addressed when and how the human/non-human primate gonad functionally develops, and whether there are replicate animal models to define gonadal function from preimplantation and conception throughout reproductive life, with a focus on prenatal and adolescent exposures.

5. Determined the roles of “environment” (socioeconomic, behavioral, nutritional, chemical and social-cultural) **on human reproductive development**, using epigenomics, genomics, proteomics, microbiome profiling, behavior and higher computational methods and generation of biomarkers.

6. Explored the role of the maternal-fetal interface with molecular characterization of embryonic and extraembryonic tissue among cohorts of at-risk populations (i.e., ART and pregnancies with maternal comorbidities, such as obesity and diabetes) related to pregnancy outcome.

7. Characterized the developmental antecedents to common reproductive “disorders” using appropriate human or animal disease models and prioritizing research on endometriosis, myomas, anovulation, infertility/subfertility, premature gonadal insufficiency, and reproductive aging.

8. Taken advantage of unique emerging populations and epidemics at a global level to address gene-environment interactions in reproductive and endocrine disorders.

9. Developed reliable assays for reproductive hormones that are widely available at reasonable cost.

What research tools, methods or approaches should be developed to achieve the anticipated outcomes?

1. Improved capacity for integrative analysis among epidemiologic, genomic/epigenomic, and phenotypic data.
2. Assured collection of data aimed at defining what is “normal,” “phenotypic variant,” and “disease” and deriving true normalization values across phenotypic strata.
3. Enable incorporation of measured environmental exposures, true normalization/reference values, genomics, and meaningful clinical outcomes, including GWAS/EWAS, transcriptomics, and interactions thereof.
4. Analyses will emphasize consideration of cellular differentiation, tissue lineage, developmental time point, and gender/race/ethnicity.
5. Include developmental psychologists in multidisciplinary teams in reproductive research to provide expertise on stress and reproductive function.
6. Assure leveraging existing or creatable resources within NIH for translational capacity: e.g., NIH Maternal Fetal Medicine Unit, Reproductive Medicine Network, Neonatal Research Network and have data and specimens readily available to all members of the scientific community in a transparent and identifiable fashion.
7. State-of –the-art approaches to functional imaging in critical windows of development.
8. Accessible and highly collaborative bioinformatics and computational resource centers of excellence with capacity for ready and transparent utilization by funded teams of investigators, in a multi-institutional capacity.
9. Clinical research or equivalent phenotyping centers to enable deep phenotyping essential to characterize normative values necessary to delineate developmental antecedents, accompanied by biorepositories of available and appropriate tissues.
10. Scalable, robust animal and cellular models for testing oligogenic variants in functional genomic assays.
11. A primate normative developmental brain atlas and brain banks using banked donated necropsy tissue.
12. Leveraged opportunity from NIH initiatives, such as the Epigenomics RoadMap, the Human Microbiome RoadMap, RAID program, ToxNet, institutional CTSA, and the like.
13. Cross cutting initiatives among NIH, OHRP, FDA, USDA, DoD, and CDC to reduce regulatory burdens and barriers to data accessibility and streamline NIH requirements to meet FDA regulatory processing.

II.4 DIAGNOSTICS AND TREATMENTS FOR IMPROVEMENT IN REPRODUCTIVE HEALTH:

Views expressed herein are the opinions of the authors and do not necessarily reflect those of the NICHD.

Introduction: The overall value and need for fundamental discovery research, prognostics, diagnostics, therapeutics and companion diagnostics that measure meaningful endpoints and targets for the therapy and inclusion of quality of life and outcomes measurements was identified and considered in the context of these opportunities. Realization of each of these broad opportunities requires integration of basic research, translational science, clinical science and medicine, and population biology research.

Scientific Opportunities: In 10 years we will have:

- 1. Conducted new mechanistic studies (basic) to enhance understanding of reproductive processes for identification of new diagnostic and/or therapeutic opportunities.*
- 2. Identified and adapted new technologies to assess reproductive health and the environment, with linkage of this information to patient history and phenotype for development of new, more efficacious treatments of reproductive disease (translational).*
- 3. Recognized that reproductive health itself is a diagnostic tool of both early embryonic and fetal life as well as a harbinger of wellness in the future (clinical).*

What basic, clinical, and translational questions need to be answered to realize these opportunities?

1. Advancement of Development and Adaptation of New Technologies for imaging and other non-invasive tools, ontogeny-based databases, analytical chemistry (including proteomics, metabolomics, metalomics, and nanotechnology), nondestructive technologies to examine single cells and to perform whole body analyses.

These technologies would then be applied, e.g., to enhance understanding of primordial follicle activation over the lifespan, develop noninvasive assessment of male and female gamete quality, and identify the most viable embryos. It will also improve understanding sex-based differences at the cellular level, including the role of inflammation in reproductive health and the relationship between the microbiome and reproductive health, as well as application of regenerative medicine approaches. Additionally, developing diagnostics applicable to early pregnancy (6 weeks) will provide the opportunity for early diagnosis and prevention of complications of ectopic pregnancy.

2. Linkage of Patient History with Phenotype to identify novel diagnostics and treatments to improve patient reproductive health. New opportunities are emerging in informatics enabling the ability to collect data and collate information related to reproductive health, linking phenotypes and biomarkers. Standardization of information collection and terminology (ontological lexicon for reproductive health), the building of public-accessible tools (R-OMIM) and strategies to harmonize this ontology with basic mechanisms and outcomes are recommended. This latter point is particularly critical, as gathering the data is one half of the equation, while data analysis that creates meaningful outcomes is the other. This will require developing appropriate biomarkers for disease and also for targeted treatments with high specificities and sensitivities.

3. Expansion of Global Reproductive Health. We believe a global reproductive health study is possible and propose to build a global infrastructure for data collection at the level of the clinic and population. This will require the development of appropriate informatics to collate large data sets and the tools to integrate information from all aspects of reproduction: maternal, fetal, and diseases of the resultant child and adult diseases of the “parents.” The global context will permit, e.g., an understanding of the lifetime burden of obesity and diabetes on reproductive health. This could also include the impact of the environment and provide unique opportunities such as understanding the wellbeing of mother and child through IVF and even the appropriate utility of IVF in unexplained subfertility, including comparative research between IVF and diagnosis-specific treatment (e.g., studies that could not easily be accomplished domestically.)

II.5. QUALITY OF LIFE (QOL)

Introduction: Quality of Life, including reproductive and sexual function, must be included in all research and clinical care. Reproductive and sexual function affects health and QOL, and health and QOL have myriad effects on reproductive and sexual function. Understanding an individual's perspective is central to optimizing QOL and innovating treatment that will facilitate understanding disease pathophysiology and effectively improve life when multiple diseases coexist. Opportunities exist for new and evolving technologies to improve data quality and capture, facilitate dissemination of information and increase the diversity of individuals participating in research and optimizing their own health.

Scientific Opportunities: In 10 years we will have:

1. *Included qualitative and quantitative assessment of QOL at baseline and throughout all clinical studies.*

Basic questions:

1. Which existing QOL tools can be used and under what circumstances?
2. What essential parameters, including context, contribute to QOL and its assessment?
3. Are the tools robust enough to capture differences in developmental stages, life circumstances, cultural and educational background, menstrual cycle variation, and the absence and presence of disease?
4. How can diversity of participants in research studies be maximized?

Research tools, methods, or approaches:

1. Include QOL assessments in all interdisciplinary, longitudinal, and population-based clinical studies.
2. Introduce new technologies for assessment, including electronic medical record capture.
3. Develop and validate new and more robust tools for QOL assessment
4. Extend a community participatory research model to reproduction studies.

2. *Developed approaches to optimize QOL outcomes for all individuals across the lifespan and assessed the impact of information available to individuals as a result of advanced technology (e.g., genetic testing, imaging, proteomics, metabolomics) on QOL.*

Basic questions:

- What variables impact most on QOL (e.g., environment, patient-provider interaction, reduction of symptoms, disease state)?
- What strategies are most effective for optimizing QOL (e.g., motivational interviewing, environmental changes, behavioral modifications)?
- How can reproducible approaches be developed and implemented for use in a variety of populations?
- How do interventions alter the natural course of disease and affect future QOL and lifelong health?
- How does the provision of genetic information or information from other advanced technologies enhance or diminish QOL?
- How does patients' use of complementary and alternative medicine impact QOL?

Research tools, methods, or approaches:

- Develops methods to track QOL over time.
- Develop ways to evaluate the information from genetic tests and other advanced technologies.

3. *Used knowledge gained from QOL assessment to optimize treatment adherence and develop novel therapeutic approaches.*

Basic questions:

- How can open communication about QOL between healthcare providers and individuals be facilitated in a time- and cost-effective manner?
- How can knowledge gained be incorporated into treatment choices?

What basic, clinical, and translational questions need to be answered to realize these opportunities?

- Develop and validate tools to determine how QOL influences adherence to therapy
- Develop approaches to integrate QOL into assessments of new therapies.

II.6. REPRODUCTIVE HEALTH AS A WINDOW TO OVERALL HEALTH

Introduction: Reproductive health addresses reproductive processes, functions, and systems throughout life and implies responsible reproduction and a responsible, satisfying, and safe sex life. It is also essential to overall wellbeing and involves the freedom to decide if, when, and how often to reproduce (WHO definition). We identified more than 100 medical conditions associated with reproductive dysfunction, including obesity, heart disease, diabetes, mood disorders, cancers, STDs, and endocrine disorders. However, the associations are poorly understood and interventions to prevent or treat these conditions are of limited or uncertain benefit.

Scientific Opportunities: In 10 years we will have completed four scientific opportunities that integrate reproductive and overall health and will have:

1. ***Created the NIH Health Care Diary***, an NIH social network database with up-to-date, prospective health data from every U.S. citizen that will employ common informational tools to collect phenotypic data from large populations, facilitate two-way real-time communications, and collect biological specimens. The network will improve phenotyping to match currently sophisticated genotyping methods, allow tracking of health issues, and inform and modify population behaviors.
2. ***Identified Natural Reproductive Biomarkers of Overall Health***: easily observable characteristics indicative of health states e.g., menstrual cycle, erectile function, BMI, and semen analysis. This opportunity will define whether natural biomarkers can be used for early disease detection and prevention and will empower populations globally to self-identify and monitor health states and status.
3. ***Reinvented Reproductive Health Clinical Trials*** by streamlining the clinical trial process for reproductive health problems and broaden participation, with the goal of significantly improving the time to design and complete trials, more rapidly translate the results to clinical care, and significantly expand the cadre of private and academic clinical investigators.
4. ***Altered Social Behaviors*** - e.g., obesity, substance abuse, alcohol use, smoking, and unsafe sex - to improve reproductive and overall health and to define relationships between behaviors and health states, develop interdisciplinary solutions to change behaviors, and empower populations to improve self-care.

These scientific opportunities are inter-connected and centered about an expanded social health network in which NIH is the hub. The social network is a database, a communication and research tool, and a resource for patients, researchers, and health care providers.

III. HOW THE SCIENTIFIC OPPORTUNITIES IN REPRODUCTION WILL ADVANCE THE NICHD MISSION.

- emphasizing that reproductive and sexual health is an integral part of optimal health and that the views and actions of the individual are essential to assess treatment outcomes and minimize harm.

Views expressed herein are the opinions of the authors and do not necessarily reflect those of the NICHD.

- establishing an atlas of normal and abnormal processes in reproduction and early development to provide insight into human (in)fertility, contraception, and consequential pregnancy and later-in-life disorders, and work toward ensuring that every person is born healthy and wanted.
- providing new insights into mechanisms underlying disease pathology and reveal fundamental links between patient history and disease. Moreover, with the right partnerships across specialties, and between academia and industry, more efficient clinical research will result, ultimately reducing the costs of clinical trials and overall health care.

IV. HOW THE SCIENTIFIC OPPORTUNITIES IN REPRODUCTION WILL AFFECT PUBLIC GLOBAL HEALTH.

Understanding when reproductive health starts and what the developmental antecedents are will enable us to define what impacts reproductive health. As a result, we will be able to optimize reproductive health outcomes of the present generation and the lifelong health of subsequent generations. On a global scale, these will enable our broader applicability and understanding across multiple racial and ethnic groups, haplotype variants, and exposure groups. Gained understanding will allow for informed interventions in a readily translatable manner and will help prioritize and focus resources to optimize health and provide effective and cost effective care. Eventually, the availability of research tools and methods to improve or prevent fertility may reduce maternal and infant mortality and morbidity worldwide, help to achieve the Millennium Development Goals, and ultimately reduce pressure on local and global natural and economic resources

V. WHAT INNOVATIVE TRAINING AND OTHER WORKFORCE DEVELOPMENT ACTIVITIES SHOULD BE PURSUED TO ADVANCE REPRODUCTIVE SCIENCE AND MEDICINE.

To achieve these goals researchers involved in clinical, basic, social and environmental science research as well as technology, informatics, epidemiology, engineering and the global health community will all need to be actively engaged in this process. http://www.who.int/mental_health/media/68.pdf

1. Improved capacity for collaborative team science, with cross talk between clinical and population-based researchers, informaticians and biostatisticians, high throughput discovery based scientists, and reductionists.
2. Research teams will include Ph.Ds cross-trained in biomedical clinical training and clinicians cross-trained in basic biomedical science.
3. Cross-disciplinary training in undergraduate and graduate/clinical education is needed in reproductive health, including: bioinformatics and biostatistics, biomedical engineering, developmental and cell biology, stem cell biology/regenerative medicine, genetics, reproductive endocrinology, epidemiology, computational biology, environmental toxicology, public and global health, biomedical ethics, immunology, and health economics; behavioral biologists; neurobiologists; ethicists with a focus on reproductive science and regulatory affairs; non-traditional research personnel including genetic counselors, physician assistants, and nurse practitioners; retention of high-throughput trained scientists (genomicists, proteomicists, etc.) in academia. Collaboration between various organizations i.e. NSF, IBM, Google, computer scientists, chemists, library science, allied health professionals, information architecture scholars, as well as all other NIH institutes where relevant is foreseen.

4. Development of innovative educational and training programs between academia, government, foundations, industry, NGOs, and advocacy organizations is recommended. Basic, translational clinical and social scientists will also need to work with one another in this new paradigm.
5. Development of on-line modules in molecular and cellular technology, as well as genomics for medical students in response to the tension between the need for increased access to primary care and the increased need for complexity with the growth of genetics and personalized medicine.
6. Fellowships and training grants targeted to contraceptive development should be implemented with a focus on basic/clinical reproductive biology, pharmaceutical development, regulatory sciences and entrepreneurship. Such programs could be implemented and funded by both the government and private sectors.
7. Creating social networks for practicing physicians to involve them in data collection and patient phenotyping.
8. Reproductive cloud-based training encouraging groups (basic reproductive trainees to work with clinical residents or fellows) to work together on a single project at distant sites with a common capstone experience at the end of the term.
9. Allowance for repayment of educational debt and/or liability insurance (i.e, “malpractice tails”).

This is an unprecedented opportunity to advance innovation in reproductive science, medicine, health, and technology, to improve the public health nationally and globally, educate, inspire, and enable the next generation, engage our community and unique partners in the novel research paradigms and teams described herein.

**NICHD Scientific Vision Workshop
on Reproduction
January 25-26, 2011
Bethesda, MD**

Participant List

Special thanks to the workshop participants, who contributed to the ideas in this white paper:

Kjersti Aagaard-Tillery, M.D.

Baylor College of Medicine
Houston, TX

Ruben Alvero, M.D.

University of Colorado School of Medicine
Aurora, CO

John K. Amory, M.D., MPH

University of Washington Medical Center
Seattle, WA

Alicia Armstrong, M.D.

Eunice Kennedy Shriver National Institute
of Child Health and Human Development
Bethesda, MD

Milan K. Bagchi, Ph.D.

University of Illinois at Urbana-Champaign
Urbana, IL

Valerie Baker, M.D.

Stanford School of Medicine
Palo Alto, CA

Jennifer S. Barber, Ph.D.

University of Michigan
Ann Arbor, MI

Kurt T. Barnhart, M.D., MSCE

University of Pennsylvania Medical Center
Philadelphia, PA

Frank M. Biro, M.D.

University of Cincinnati College of
Medicine
Cincinnati, OH

Robert Blelloch, M.D., Ph.D.

University of California, San Francisco
San Francisco, CA

Paul D. Blumenthal, M.D., MPH

Stanford School of Medicine
Palo Alto, CA

William J. Bremner, M.D., Ph.D.

University of Washington School of
Medicine
Seattle, WA

Serdar E. Bulun, M.D.

Northwestern University
Chicago, IL

Karen Casey

Eunice Kennedy Shriver National Institute
of Child Health and Human Development
Bethesda, MD

Marcelle Cedars, M.D.

University of California, San Francisco
San Francisco, CA

Streamson C. Chua, Ph.D.

Albert Einstein College of Medicine
Bronx, NY

PonJola Coney, M.D.

Virginia Commonwealth University School
of Medicine
Richmond, VA

Marco Conti, M.D.

University of California, San Francisco
San Francisco, CA

Christos Coutifaris, M.D., Ph.D.

University of Pennsylvania
Philadelphia, PA

William Crowley, M.D.

Harvard Medical School/Massachusetts
General Hospital
Boston, MA

Philip Darney, M.D., M.Sc.

University of California, San Francisco
San Francisco, CA

Louis De Paolo, Ph.D.

Eunice Kennedy Shriver National Institute
of Child Health and Human Development
Bethesda, MD

Franco DeMayo, Ph.D.

Baylor College of Medicine
Houston, TX

S.K. Dey, Ph.D., M.Sc.

University of Cincinnati College of
Medicine
Cincinnati, OH

Andrea Dunaif, M.D.

The Feinberg School of Medicine,
Northwestern University
Chicago, IL

Asgi T. Fazleabas, Ph.D.

Michigan State University College of
Human Medicine
East Lansing, MI

Susan J. Fisher, Ph.D.

University of California, San Francisco
San Francisco, CA

Linda C. Giudice, M.D., Ph.D.

University of California, San Francisco
San Francisco, CA

Louis J. Guillette, Ph.D.

Medical University of South Carolina
Charleston, SC

Paula Hillard, M.D.

Stanford University Medical Center
Stanford, CA

Jeffrey T. Jensen, M.D., MPH

Oregon Health and Sciences University
Portland, OR

Gregory S. Kopf, Ph.D.

Kansas University Medical Research
Institute
Kansas City, KS

Andrew La Barbera, Ph.D., HCLD

American Society of Reproductive Medicine
Birmingham, AL

Dolores J. Lamb, Ph.D.

Baylor College of Medicine
Houston, TX

Richard S. Legro, M.D.

Penn State Milton S. Hershey Medical
Center
Hershey, PA

Christopher R. McCartney, M.D.

University of Virginia School of Medicine
Charlottesville, VA

Diane F. Merritt, M.D.

Washington University in St. Louis School
of Medicine
St. Louis, MO

Ben Mol, M.D., Ph.D.

Academic Medical Center
Amsterdam, Netherlands

Kelle H. Moley, M.D.
Washington University in St. Louis School
of Medicine
St. Louis, MO

Bert W. O'Malley, M.D.
Baylor College of Medicine
Houston, TX

Vasantha Padmanabhan, Ph.D.
University of Michigan
Ann Arbor, MI

Stephanie T. Page, M.D., Ph.D.
University of Washington Medicine
Seattle, WA

Stephen S. Palmer, Ph.D.
EMD-Serono Research Institute
Rockland, MA

Catherine Racowsky, Ph.D.
Brigham and Women's Hospital; Harvard
Medical School
Boston, MA

Aleksandar Rajkovic, M.D., Ph.D.
University of Pittsburgh
Pittsburgh, PA

Robert William Rebar, M.D.
University of Alabama Birmingham
Birmingham, AL

Renee A. Reijo-Pera, Ph.D.
Stanford University School of Medicine
Stanford, CA

Gloria Richard-Davis, M.D.
Meharry Medical College
Nashville, TN

Emilie F. Rissman, Ph.D.
University of Virginia Medical School
Charlottesville, VA

Robert Rosenfield, M.D.
University of Chicago
Chicago, IL

Susan L. Rosenthal, Ph.D.
Columbia School of Medicine
New York, NY
Carmen Sapienza, Ph.D.
Temple University School of Medicine
Philadelphia, PA

Stephanie Beth Seminara, M.D.
Massachusetts General Hospital; Harvard
University Medicine
Boston, MA

Régine Sitruk-Ware, M.D.
Population Council
New York, NY

Elizabeth G. Stewart, M.D.
Mayo Clinic and Mayo Medical School
Rochester, MN

Richard L. Stouffer, Ph.D.
Oregon Health and Science University
Beaverton, OR

Jerome F. Strauss, M.D., Ph.D.
Virginia Commonwealth University School
of Medicine
Richmond, VA

James Trussell, Ph.D.
Princeton University
Princeton, NJ

Paul Jacob Turek, M.D.
The Turek Clinic
San Francisco, CA

Teresa K. Woodruff, Ph.D.
The Feinberg School of Medicine,
Northwestern University
Chicago, IL