



Treatment Options for Uterine Fibroids

Ad hoc Workgroup Meeting

March 5th, 2013

Patient-Centered Outcomes Research Institute



Welcome and Introductions

Patient-Centered Outcomes Research Institute



Joe V. Selby, PCORI



David Hickam, PCORI

Patient-Centered Outcomes Research Institute

Housekeeping: Providing Input

- Today's webinar participants can provide input via email (fibroids@pcori.org); via Twitter (using #PCORI); the webinar "chat" feature; through our webpage "Submit a Question on our Targeted Topics for Research Funding;" and during the upcoming public comment period, by telephone.
- Please submit questions today as they occur to you. We will collect and synthesize these for discussion at 1:15 pm ET.
- If you want to comment by phone, we'll open the lines during the comment period at 12:15 pm ET and provide instructions at that time.
- We welcome additional input through 5 pm ET March 19 via the webpage noted above and email (fibroids@pcori.org).

Introductions: Chair and Moderator

- **James H. Segars, MD**, is head of Unit on Reproductive Endocrinology within the Reproductive Biology and Medicine Branch of NICHD at NIH and Associate Professor of Obstetrics and Gynecology at the Uniformed Services University of the Health Sciences.

Introductions: Researchers

- **Evan Myers, MD, MPH (Duke University)**
 - Information gaps related to health disparities in uterine fibroids, and the comparative effectiveness of outcomes for different subpopulations.
- **Cynthia Morton, PhD (Harvard Medical School)**
 - Information gaps related to the differences in fibroid disease and how these differences impact research.
- **Linda Bradley, MD (Cleveland Clinic)**
 - Information gaps related to surgical options for uterine fibroids.
- **Bijan Borah, PhD (Mayo Clinic)**
 - Information gaps regarding non-surgical options including UAE, MRI guided ultrasound, and others.

Introductions: Patient Advocates

Elizabeth Battaglino

- Chief Executive Officer, HealthyWomen.com

Keshia Cheeks

- Patient Advocate

Sateria Venable

- Founder, The Fibroid Initiative

Hope Waltman

- Founder, Hope for Fibroids

Introductions: Other Stakeholders

Edward Evantash, MD

- Medical Director, Vice President of Medical Affairs, Hologic

Deborah Bradley Kilstein, RN, MBA, JD

- Vice President, Quality Management and Operational Support, Association of Community Affiliated Plans

Sergio Rimola, MD

- National Hispanic Medical Association

Jeffery M. Rothenberg, MD

- American Congress of Obstetricians and Gynecologists

James Spies, MD

- Fellow, Society for Interventional Radiology



Background on Ad hoc Workgroups

Patient-Centered Outcomes Research Institute



Joe V. Selby, PCORI



David Hickam, PCORI

Patient-Centered Outcomes Research Institute

About PCORI

- An independent non-profit research organization authorized by Congress as part of the 2010 Patient Protection and Affordable Care Act (ACA).
- Committed to continuously seeking input from patients and a broad range of stakeholders to guide its work.

PCORI's Mission and Vision

Mission

The Patient-Centered Outcomes Research Institute (PCORI) helps people make informed health care decisions, and improves health care delivery and outcomes, by producing and promoting high integrity, evidence-based information that comes from research guided by patients, caregivers and the broader health care community.

Vision

Patients and the public have the information they need to make decisions that reflect their desired health outcomes.

PCORI's First Targeted Research Topics

- Identified five high-priority, stakeholder-vetted topics.
- Jumpstarts PCORI's long-term topic generation and research prioritization effort.
- Builds on similar, earlier efforts by others.
- Allows us to build on our engagement work.

Treatment Options for Uterine Fibroids

Treatment Options for Severe Asthma in African-Americans and Hispanics/Latinos

Preventing Injuries from Falls in the Elderly

Treatment Options for Back Pain

Obesity Treatment Options in Diverse Populations

Targeted PFA Workgroup Goals

Obtain input from researchers, patients, and other stakeholders.

Identify high-impact research questions that will result in findings that are likely to endure and are not currently studied.

Understand the potential for research to lead to rapid improvement in practice, decision-making, and outcomes.

Confirm the importance and timeliness of particular research topics.

Seek consensus on identified knowledge gaps and specific questions within those topics.

Provide summary
of findings to
Board of
Governors

Workgroup Objectives: A Narrowing Process

- Consider the broad range of research questions provided by researchers, patients, and other stakeholders.
- Narrow questions to determine which are most critical.
- Narrow further by identifying a concise list of high-priority questions.

Criteria for Knowledge and Research Gaps

Knowledge gaps should:

- **Be patient-centered:** Is the proposed knowledge gap of specific interest to patients, their caregivers, and clinicians?
- **Assess current options:** What current guidance is available on the topic and is there ongoing research? How does this help determine whether further research is valuable?
- **Have potential to improve care and patient-centered outcomes:** Would new knowledge generated by research be likely to have an impact in practice?
- **Provide knowledge that is durable:** Would new knowledge on this topic remain current for several years, or would it be rendered obsolete quickly by subsequent studies?
- **Compare among options:** Which of two or more options lead to better outcomes for particular groups of patients?

Questions External to PCORI's Mandate

- **Cost effectiveness:** PCORI will consider the measurement of factors that may differentially affect patients' adherence to the alternatives such as out-of-pocket costs, but cannot fund studies related to cost-effectiveness, costs of treatments or interventions.
- **Medical billing:** PCORI cannot fund studies about an individual's personal insurance coverage or about coverage decisions from third party payers.
- **Disease-processes and causes:** PCORI cannot fund studies that pertain to risk factors, origin and mechanisms of diseases.

How PCORI Gathers Input

PCORI distinguishes “input” to the PFA development process from “involvement” in the process.

Input is information that may or may not be considered or used in crafting The PFA. Involvement is the activity of determining what will be in the PFA.

- The researchers, patients and stakeholders who've been invited to this workgroup give input during the workgroup.
- The broad community of researchers, patients and other stakeholders can give input via our website – for the past four weeks and for the next two.
- Webinar participants can provide input via email (fiborids@pcori.org); Twitter (hashtag #PCORI); the webinar “chat” feature; the “Submit a Question on our Targeted Topics” webpage; and, during the upcoming public comment period, by phone.

How PCORI Manages the Potential for Conflicts of Interest

- Participants in this workgroup will be eligible to apply for funding if PCORI decides to produce a funding announcement on treatment options for uterine fibroids
- The Chair of this workgroup will not be eligible.
- Input received during the workgroup deliberations are broadcast via webinar, and the webinar is then archived and available to other researchers, patients or stakeholders on the website.
- PCORI does not have subsequent discussions with the presenters after this workgroup.
- Presenters have been explicitly instructed and are expected to address a set of questions we've asked – not to tell us about their research.
- There should be no “influence advantage” to being a workgroup member, nor any knowledge advantage as to what will eventually be requested in the PFA.



Setting the Stage

Patient-Centered Outcomes Research Institute



Setting the Stage



James H. Segars, MD
National Institute of
Child Health and Development

Patient-Centered Outcomes Research Institute

Overview

- Populations affected and public health view
- Patient perspectives of fibroid disease
- Treatment options for uterine fibroids
- Objectives for workgroup: information gaps
- Sample questions and research areas of interest

Background on Uterine Fibroids: *Populations Affected*

- Uterine fibroids are present in roughly one-in-two women in the United States
 - About 20% of women of childbearing age develop uterine fibroids
 - By age 50, 70% of white women and 80% of African-American women develop fibroids

Background on Uterine Fibroids: *Populations Affected (continued)*

- African-American women are disproportionately affected:
 - Increased prevalence in young women (25%), middle-aged (50%), and older women (up to 80%)
 - Women over age 45: fibroid growth rates decrease in white, but not in African-American women

Background on Uterine Fibroids: *Public Health Burden*

- Estimated costs, including pregnancy-related costs:

\$34 billion annually in the United States

...on par with the combined costs of breast, colon, and ovarian cancers in the United States

Background on Uterine Fibroids: *Burden of Disease for Patients*

- Pain
- Cramping
- Heavy menstrual bleeding
- Anemia
- Reproductive complications
 - Infertility
 - Miscarriage
 - Preterm labor
 - Sterility
 - Others
- Uterine fibroids may be asymptomatic

Uterine Fibroids: *Patient Profiles*

42-year-old African-American woman, one child.

Uterine artery embolization for bleeding three years ago. Past three years: three hospitalizations for blood transfusion.

Uterus one inch above navel. Anemic with symptoms. At wit's end. Managed with GnRH agonist therapy for six months. Hysterectomy at age 42; uterus with many fibroids.



Uterine Fibroids: *Patient Profiles (continued)*

“I am 73 years old. Persons my age look back upon life and weigh pleasures and disappointments, joys and sadness, and satisfactions and regrets. My greatest regret is that I never had children of my own. I never had children because I lost the capacity to bear children. A large fibroid causing great pain, pressure, and debilitating bleeding necessitated a hysterectomy in my thirties.”

Background on Uterine Fibroids: *Treatment Considerations*

- Treatment of uterine fibroids can be complex because:
 - Fibroids can be located in any part of the uterus
 - Multiple fibroids can reside in one uterus
 - Fibroids can be different sizes
 - Fibroid disease varies in severity (some uteri are replete with tumors)

Background on Uterine Fibroids: *Treatment Considerations (continued)*

- Treatment of uterine fibroids can be complex because:
 - Fibroids have variable growth rates: some grow, others are stable, some shrink spontaneously
 - There is no universally accepted classification system
 - Symptoms vary: treatments for bleeding and pain may differ from fertility treatments
 - Outcomes vary: some studies focused only on bleeding outcomes; other outcomes are important—pain, fertility, re-intervention (UFS-QOL vs. hemoglobin)

Background on Uterine Fibroids: *Treatment Options (least to more invasive)*

- Watchful waiting

- Pain medication

- Hormone therapy

- GnRH agonist/antagonists (medical menopause)
- Progesterone-blocking agents (ulipristal, mifepristone)
- Aromatase-blocking agents (letrozole)
- Progestin-only pill
- Oral contraceptive pills

- Intrauterine device (Mirena)

- Minimally invasive options

- Uterine artery embolization
- MRI-guided focused ultrasound
- Hysteroscopic/laparoscopic resection
- Other strategies

Background on Uterine Fibroids: *Treatment Options (continued)*

- Myomectomy

- Hysterectomy

- Over 200,000 women with uterine fibroids receive hysterectomies annually in the United States
- Many of these women are of childbearing age

Background on Uterine Fibroids: *Information Gaps*

- What is the natural history of fibroids in young African-American women?
- Are there any effective treatments for young women to prevent fibroids or promote regression?
- Can diet, vitamins (D3), or green tea extracts (EGCg) prevent or benefit fibroid disease?
- What are the best treatment options for women with severe symptoms or disease who want to bear children?

Background on Uterine Fibroids: *Information Gaps (continued)*

- Which treatment strategies work best for women of different races and ethnicities?
- How safe and effective are the newest technologies for the treatment of uterine fibroids?
- Is uterine fibroid treatment less effective for African-American women than for other women who are getting fertility services?

Background on Uterine Fibroids: *Research Areas of Interest*

- Questions on the staging of treatments, including the pharmacotherapeutic options as initial therapy, on durability of symptom relief and patient-reported outcomes
- Questions that identify and compare promising strategies to identify and choose treatment options for fibroid management, including those tailored for different subpopulations
- Questions may focus on different segments of reproductive-age women who are affected by differing symptom severity, reproductive preferences, or involve patients with additional risk factors



Background on Uterine Fibroids: *Research Areas of Interest (continued)*

- Questions that compare interventions to evaluate the relative effectiveness of the available procedural or nonprocedural treatments for uterine fibroids
- Questions that address the relative effectiveness of procedural treatments (e.g., hysterectomy, myomectomy, uterine artery embolization, MRI-guided focused ultrasound, endometrial ablation) on durability of symptom relief and patient-reported outcomes



Researcher Presentations

Patient-Centered Outcomes Research Institute



Evan R. Myers, MD, MPH

Duke University

Patient-Centered Outcomes Research Institute

Critical Gaps in Evidence: Disparities

- Burden of disease associated with fibroids substantially higher in African-American women compared to white women (limited data on other racial/ethnic groups)
 - African-American women more likely to have:
 - Procedures performed at younger ages (true for UAE, myomectomy, as well as hysterectomy)
 - Larger, more numerous fibroids
 - More severe symptoms
 - More acute complications of procedures
 - Greater risk of complications appears to be largely attributable to differences in uterine anatomy, greater prevalence of other risk factors for complications

Critical Gaps in Evidence: Disparities

Possible explanations

- Biological/genetic differences in fibroid growth
 - Fibroids and keloids
- Differences in environmental exposures
- Differences in quality of care
 - But complication rates similar after adjustment for differences in uterine anatomy, other risk factors
- Differences in access to care
 - Lack of insurance could lead to more severe disease by time procedures are performed (analogous to breast, cervical cancer)
 - But no evidence that earlier medical treatment effective
- Differences in patient thresholds for seeking care or provider thresholds for offering care

Potential New Research Area: Disparities

Broad Research Question

- Are there patient, provider, and/or health system characteristics that contribute to more “advanced” fibroids at time of treatment in African-American women?
 - Larger, more numerous fibroids associated with higher risk of short-term complications → Earlier treatment might decrease these complications
 - Some studies can be done now, but future research would be made much easier if there were accepted, validated, easily coded “staging system” for fibroids
 - Changes in practice
 - Patients → If threshold for seeking care different, could potentially be justification for screening in some patients
 - Providers → Revised guidelines
 - System → Increased access to providers
 - Changes would be long-term
 - Appropriate strategies might be modified by effective medical treatments, identification of biomarkers of increased risk

Justification for Disparities: Access to Care

| | |
|-----------------------|--|
| Question | <ul style="list-style-type: none">Do differences in the availability of coverage for treatment of symptomatic fibroids affect the risk of complications in women undergoing invasive treatments (hysterectomy, myomectomy, UAE)? |
| Population | <ul style="list-style-type: none">Women undergoing these procedures whose primary coverage is Medicaid |
| Research Need | <ul style="list-style-type: none">African American women more likely to have complications of treatment, partly because of more severe disease at treatmentUnclear extent to which more severe disease is a function of biological/environmental differences versus differences in careIdentifying contribution from differences in care could lead to changes in practice/policy that would reduce short-term morbidityMedicaid covers small proportion of cases (7%), but disproportionately African American, higher complications |
| Proposed Study | <ul style="list-style-type: none">Thresholds for Medicaid coverage vary by stateSurgical complications (bleeding, injury to organs) surrogate for “degree of difficulty” due to fibroid size, numberHypothesis: If access to care is contributor to more severe disease at time of treatment, complication rates should be highest in states with highest threshold for Medicaid eligibilityStudy: Compare complication rates among Medicaid recipients (stratified by race) as a function of state Medicaid eligibility criteria (e.g., percentage federal poverty level), controlling for codable risk factorsLong term: Follow for changes, variation in complication rates as ACA is implemented |
| Timeline | <ul style="list-style-type: none">One to two years for existing Medicaid data, with planned extension as ACA is implemented |
| Cost | <ul style="list-style-type: none">Low |

Critical Gaps in Evidence: Subpopulations Symptoms

- Fibroids associated with range of symptoms
 - Heavy uterine bleeding
 - Pain (both cyclic and non-cyclic)
 - Pressure symptoms
 - Urinary symptoms
 - Painful intercourse
 - Reproductive issues
- Type, severity of symptoms affected by size, location, number of fibroids
 - But relationship not consistent

Critical Gaps in Evidence: Subpopulations Symptoms

- Change in fibroid size common outcome for studies of non-surgical treatments
 - Questionable relevance as patient-centered outcome
- Some disease-specific quality-of-life measures available
 - Currently no patient-reported outcome measure accepted by FDA for studies of medical treatment
 - For treatment of bleeding, physical measurement of blood loss acceptable, but not patient-reported measure of burden
- Little data on comparative effectiveness of different treatment options based on patient-specific symptoms

Potential New Research Area: Symptoms

- Does the comparative effectiveness of available treatments for symptomatic uterine fibroids differ based on a patient's specific symptoms?
 - Key preliminary research step: standardized measures for reporting symptoms, symptom severity
 - Reported as part of standard of care (EMRs)
 - Long-term change: choice of treatment would vary based on particular symptoms
 - No different from other conditions
 - Example: New medical treatment might resolve bleeding symptoms but not pressure or pain

Critical Gaps in Evidence: Subpopulations Reproductive Outcomes

- Fibroids associated with range of adverse reproductive outcomes
 - Infertility (?)
 - Miscarriage
 - Preterm birth
 - Breech/other malpresentation
 - Cesarean delivery
- Multiple potential sources for bias
 - Risk factors for fibroids (older age, African-American) also risk factors for adverse reproductive outcomes
 - Fibroids more likely to be detected in complicated pregnancies (more ultrasounds, c-sections)

Critical Gaps in Evidence: Subpopulations Reproductive Outcomes

- Desire to preserve ability to have children important consideration in treatment choice, but little data on comparative outcomes
 - Older age → Pregnancy rate lower, miscarriage rate higher
 - Consistent evidence suggesting some treatments affect ovarian function → Decreased pregnancy rate, earlier menopause
 - Common risk factors for fibroids, adverse pregnancy outcomes
 - Low absolute number of women trying/achieving pregnancy in reported studies
 - Relatively short follow-up
 - Highly mobile population creates challenges for follow-up

Potential New Research Area: Reproductive Outcomes

- Do reproductive outcomes (ovarian function, fecundity, pregnancy complications) differ between different alternatives to hysterectomy for symptomatic fibroids?
 - Currently little data, so any evidence would help patients and providers in decision making
 - Desire for pregnancy relative contraindication for some options (focused ultrasound) despite lack of data
 - Any specific medical therapy likely to either make pregnancy less likely (through hormonal effects) or be potentially teratogenic (through effects on tissue growth/differentiation), so procedural treatments likely to be primary option for women desiring pregnancy

Justification for Reproductive Outcomes

| | |
|-----------------------|---|
| Question | <ul style="list-style-type: none">What is the comparative likelihood of specific reproductive outcomes (ability to get pregnant, live birth, preterm birth, cesarean section) following non-hysterectomy invasive treatments for symptomatic fibroids? |
| Population | <ul style="list-style-type: none">Women undergoing treatment with myomectomy, UAE, focused ultrasound who state plans for pregnancy within five years of procedure |
| Research Need | <ul style="list-style-type: none">Uncertain whether different alternatives to hysterectomy affect probability of (a) getting pregnant, and (b) having a complication of pregnancyMay be trade-offs between effectiveness in terms of relief of specific symptoms and likelihood of optimal reproductive outcomesBetter data would help patients and providers in making decisions about treatment options |
| Proposed Study | <ul style="list-style-type: none">National registry of women undergoing any of these proceduresRegular follow-up (given high mobility in younger patient population, will require more resources for follow-up) via survey (online/mail/phone)Medical records for pregnancy-related events |
| Timeline | <ul style="list-style-type: none">Five to 10 years |
| Cost | <ul style="list-style-type: none">Moderate-to-high (primarily need for large numbers, extra efforts to ensure high retention) |



Cynthia C. Morton, PhD

Brigham and Women's Hospital
and Harvard Medical School

Patient-Centered Outcomes Research Institute

Critical Gaps in Evidence

- Despite recognition of a genetic risk to develop uterine fibroids, there is little knowledge of underlying risk alleles
- Although genetic heterogeneity is recognized between ethnic groups, the molecular basis is unknown
- Noninvasive methods are not available to diagnose uterine fibroid genetic subtypes

Potential New Research Area

Question #1:

What interventions using genetic diagnostics can identify women who are more likely to develop uterine fibroids?

Justification for Question #1

| | |
|-----------------------|---|
| Question | <ul style="list-style-type: none">• What interventions using genetic diagnostics can identify women who are more likely to develop uterine fibroids? |
| Population | <ul style="list-style-type: none">• All women with uterine fibroids |
| Research Need | <ul style="list-style-type: none">• Family medical histories inclusive of a history of uterine fibroids |
| Proposed Study | <ul style="list-style-type: none">• Women with uterine fibroids would be taught to use the U.S. Surgeon General's My Family Health Portrait (https://familyhistory.hhs.gov/fhh-web/home.action) to inform healthcare providers of a genetic risk and potential for future development of additional uterine fibroids. Family medical histories would have the added value of educating women about the heritability of uterine fibroids and would inform healthcare providers of many other medical conditions. |
| Timeline | <ul style="list-style-type: none">• Implementation of family medical histories with specific information on uterine fibroids can be performed currently with existing electronic tools |
| Cost | <ul style="list-style-type: none">• Costs include integration of family medical histories into medical visits for uterine fibroids |

My Family Health Portrait

A tool from the Surgeon General

Using *My Family Health Portrait* you can:

- Enter your family health history.
- Print your family health history to share with family or your health care worker.
- Save your family health history so you can update it over time.

Talking with your health care worker about your family health history can help you stay healthy!

[Learn more about *My Family Health Portrait*](#)

[Create a Family Health History](#)

[En Español](#)

[Use a Saved History](#)

[Em Português](#)

[In Italiano](#)



<https://familyhistory.hhs.gov>



Your Personal Information (press to hide)

[Get Help](#)

We start the family health history with you. Enter the required personal information and your health history information. At the bottom of the page (you may need to scroll), press the "Next" button. You will then be asked to tell the system which family members you would like to add to the health history.

If you have a Microsoft® HealthVault™ account, you can choose to copy your HealthVault family history information into this website. Information that you add or modify here can then be copied back to HealthVault. Press "Copy from HealthVault" to get started.

[Copy FROM !\[\]\(75f5fa6c53ae03e669fc3d7e4af55ae1_img.jpg\) HealthVault](#)

*Indicates required information.

Name:

***Gender:** Male Female

***Date of Birth:**

mm/dd/yyyy

Were you born a twin? No Yes - Identical (Same) Yes - Not Identical (Fraternal)

Were you adopted? Yes

Height: Feet Inches **-OR-** Centimeters

Weight: lbs

Your Health Information

[Get Help](#)

In the list below, select a **Disease or Condition** (if any) from the dropdown box. Then select the **Age at Diagnosis** and press the **Add** button. You may repeat this process as necessary.

| Disease or Condition | Age at Diagnosis | Action |
|---|--|------------------------------------|
| <input type="text" value="Other - Add New"/> | <input type="text" value="--Select Age at Diagnosis--"/> | <input type="button" value="Add"/> |
| <input type="text" value="Uterine Fibroids"/> | <input type="text" value="--Select Age at Diagnosis--"/> | <input type="button" value="Add"/> |

Potential New Research Area

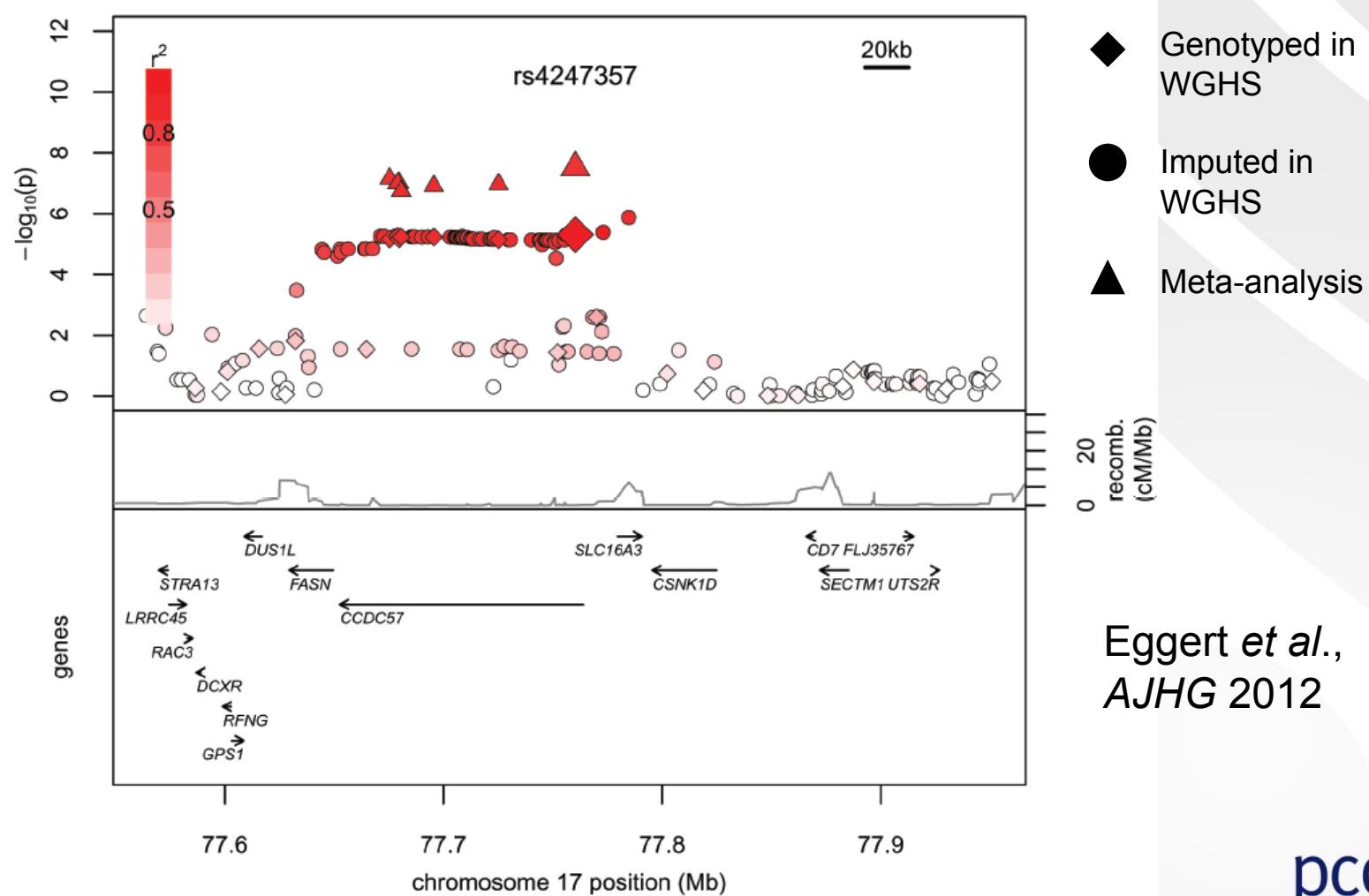
Question #2:

What comparative studies using genome-wide association studies (GWAS) and meta-analyses of existing data could lead to tests of targeted therapies?

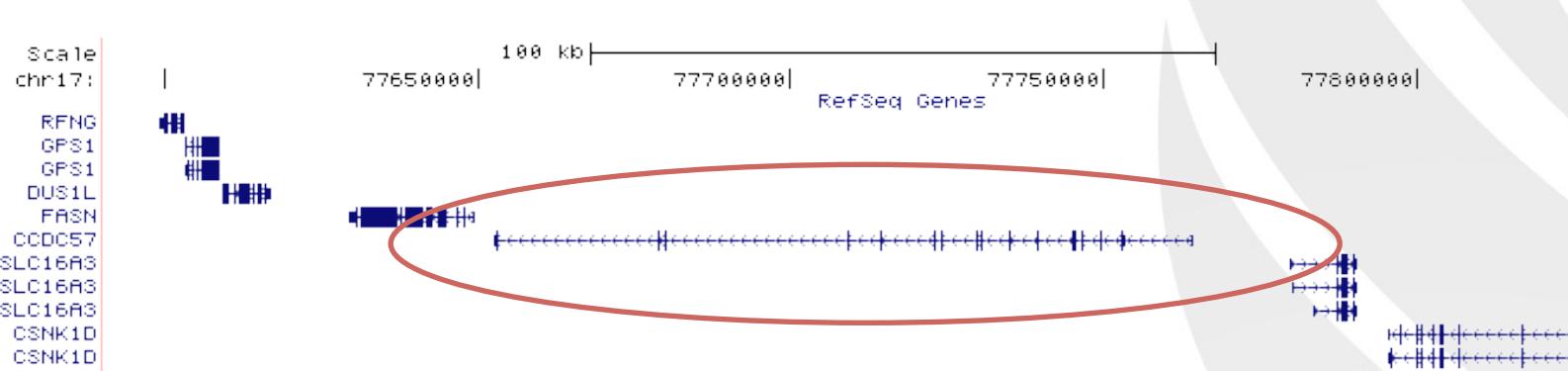
Justification for Question #2

| | |
|-----------------------|--|
| Question | <ul style="list-style-type: none">What comparative studies using genome-wide association studies (GWAS) and meta-analyses of existing data could lead to tests of targeted therapies? |
| Population | <ul style="list-style-type: none">Genotyped cohorts with medical history information on uterine fibroids |
| Research Need | <ul style="list-style-type: none">Additional genetic analyses to improve the power to identify risk alleles for which existing drugs may be repurposed or developed |
| Proposed Study | <ul style="list-style-type: none">GWAS on existing cohorts with medical history information on uterine fibroids, surveying additional genotyped cohorts for medical history of uterine fibroids and meta-analysis of all cohort data |
| Timeline | <ul style="list-style-type: none">One to two years to organize groups with data, to obtain medical histories of fibroids from other cohorts, and to perform meta analysis |
| Cost | <ul style="list-style-type: none">Personnel to organize a consortium and geneticist to perform statistical analysis |

Significant SNPs on Chromosome 17



Candidate Genes



Fatty acid synthase (*FASN*)

- Responsible for *de novo* fatty acid synthesis
- Up-regulated in several cancers

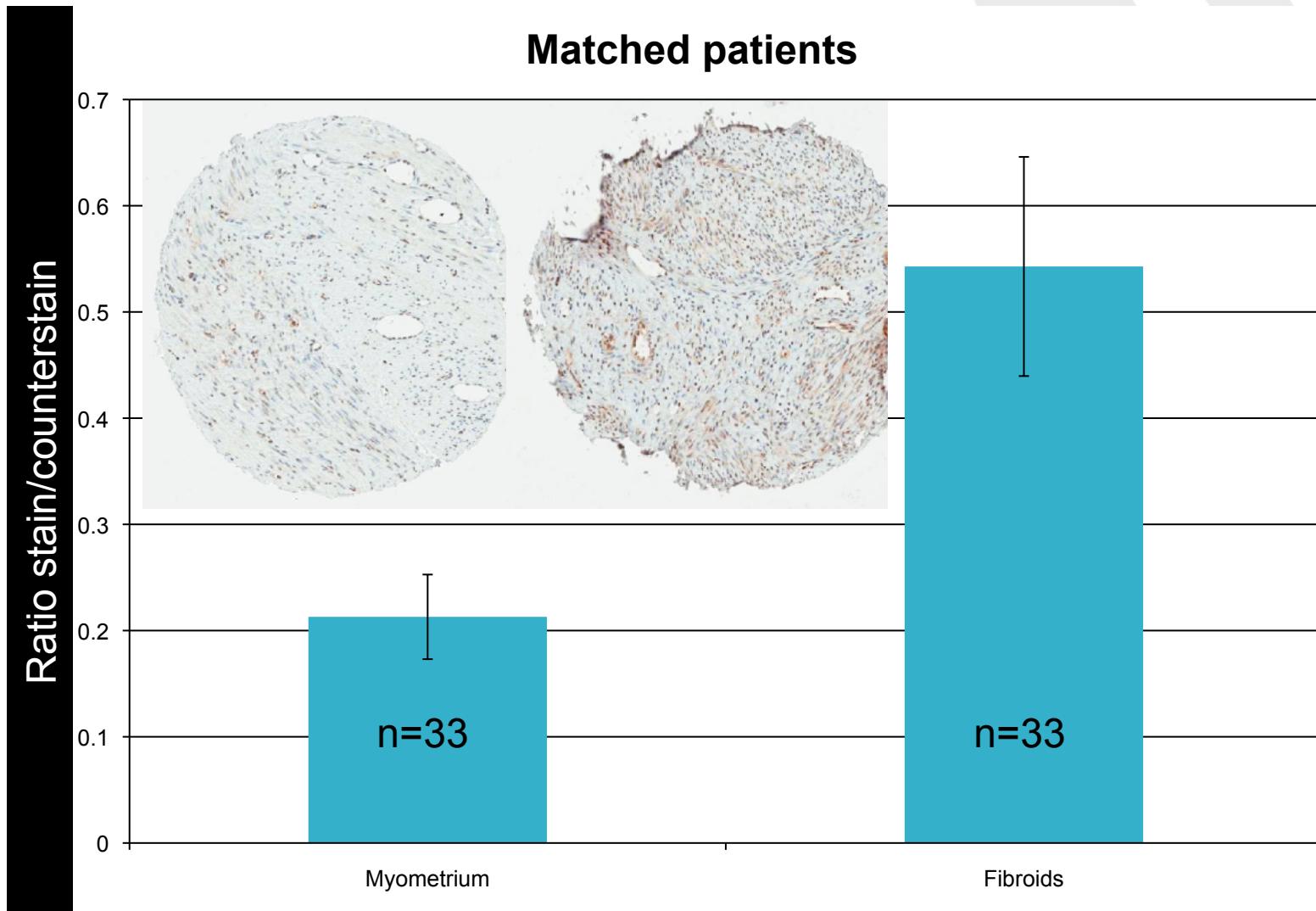
Coiled-coil domain containing 57 (*CCDC57*)

- Contains a coiled coil domain for binding DNA

Solute carrier family 16, member 3 (*SLC16A3*)

- Facilitates transport of substrates across the plasma membrane

FAS Protein Levels



FAS Therapies

- Inhibitors of FAS selectively kill cancer cells and slow growth of tumors in prostate cancer xenograft models
- FAS inhibitors in rat and mouse models of breast cancer delay development and slow progression
- How do inhibitors affect fibroid and myometrium cells?

Potential New Research Area

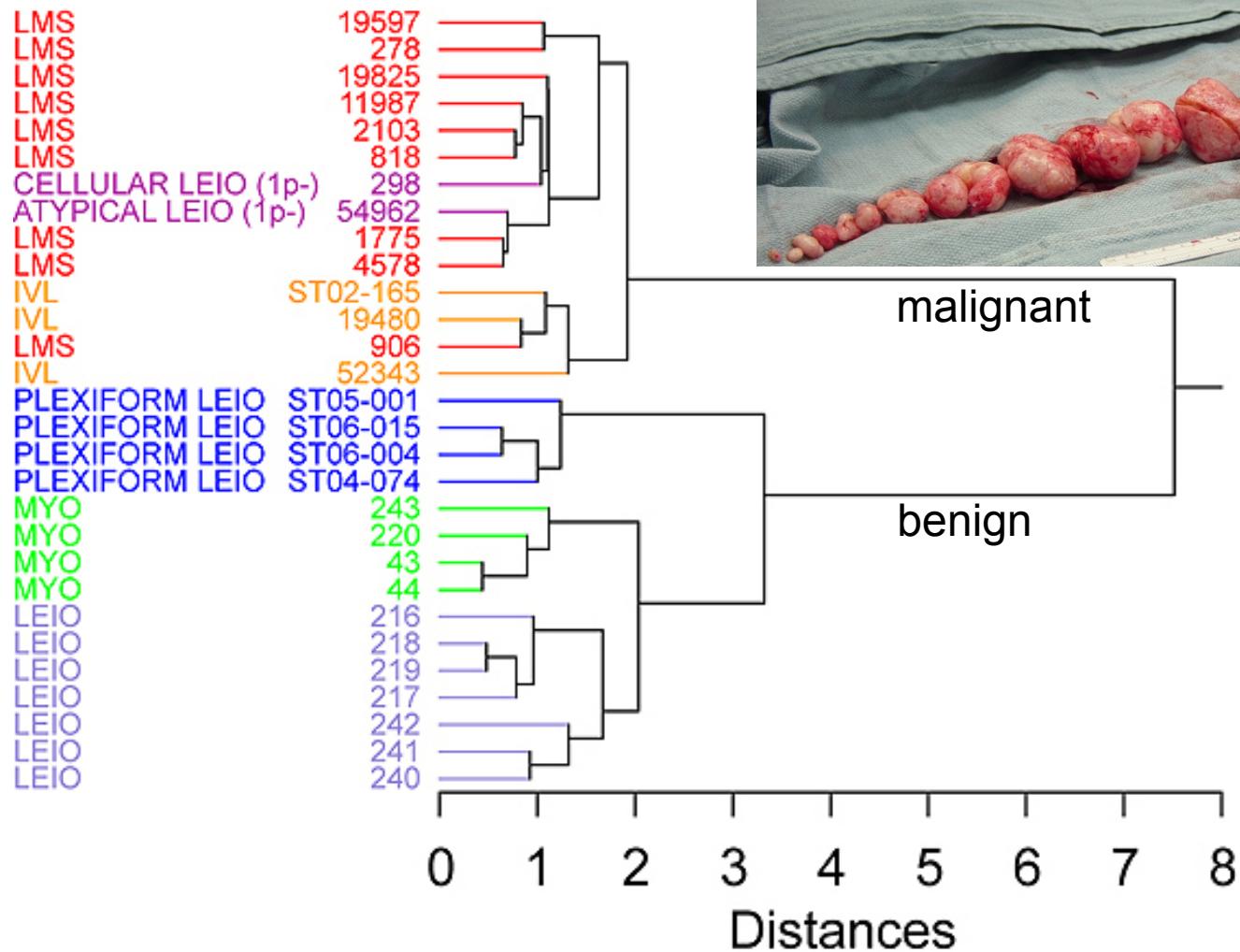
Question #3:

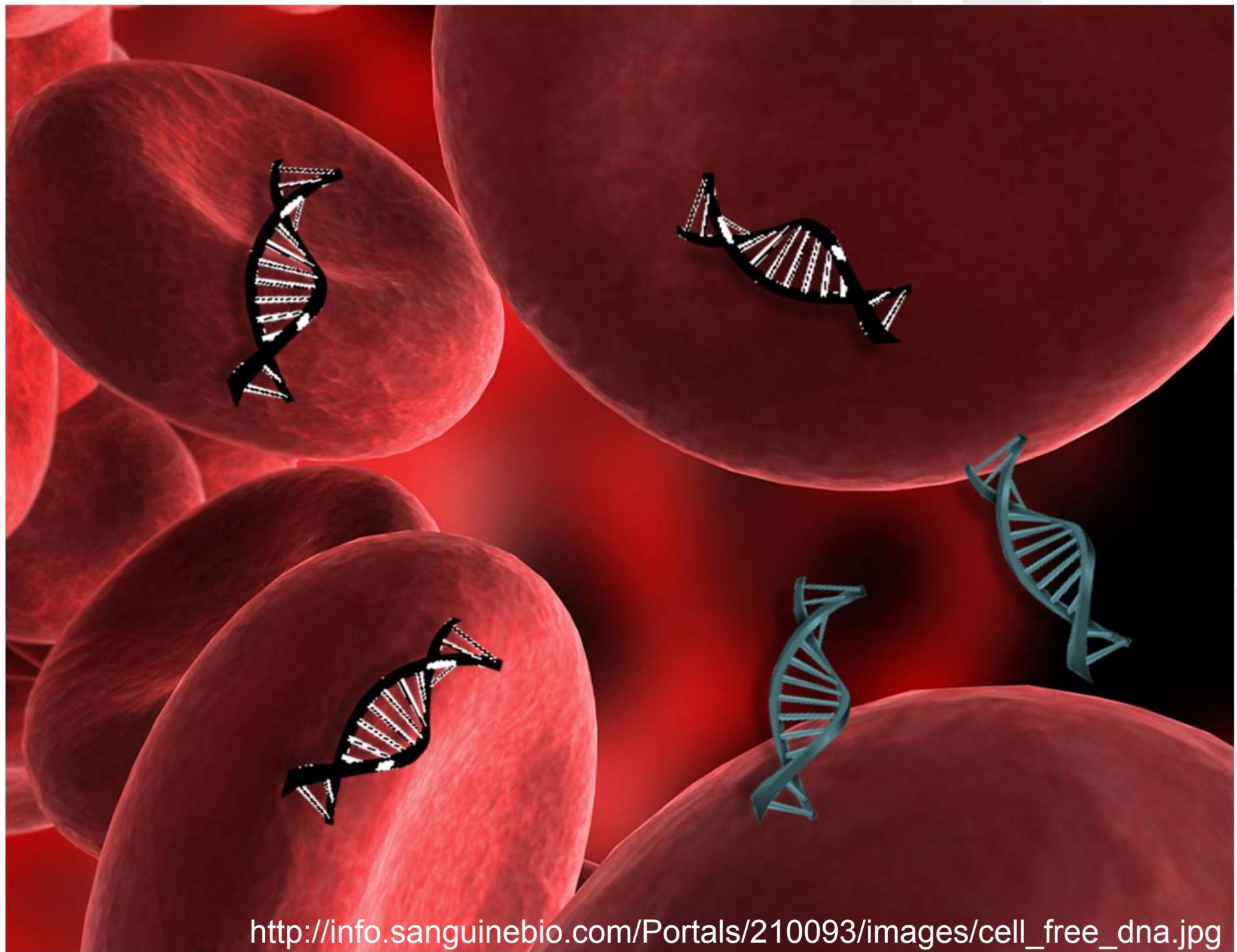
Which comparative diagnostic interventions studies using genetic subtypes from cell-free DNA could predict tumor behavior?

Justification for Question #3

| | |
|-----------------------|---|
| Question | <ul style="list-style-type: none">Which comparative diagnostic interventions studies using genetic subtypes from cell-free DNA could predict tumor behavior? |
| Population | <ul style="list-style-type: none">All women with uterine fibroids |
| Research Need | <ul style="list-style-type: none">A noninvasive diagnostic method to assess genetic changes in uterine fibroids that are prognostic |
| Proposed Study | <ul style="list-style-type: none">Paired peripheral blood samples and tumors for genetic analyses assessing genomic copy number based on existing data from cytogenetic studies with future patient management based on noninvasive screening |
| Timeline | <ul style="list-style-type: none">Testing available with current platforms underway routinely in prenatal diagnosis for aneuploidy screening and in pilot studies for neoplasms (other than fibroids) |
| Cost | <ul style="list-style-type: none">Fee schedules available for commercial services for cell-free DNA and commercial and academic cores SNP analyses |

Uterine Fibroids Are Heterogeneous Tumors





http://info.sanguinebio.com/Portals/210093/images/cell_free_dna.jpg



Ten Minute Break

Patient-Centered Outcomes Research Institute



Researcher Presentations

Patient-Centered Outcomes Research Institute



Linda D. Bradley, MD
Cleveland Clinic

Patient-Centered Outcomes Research Institute

Critical Gaps in Evidence

- Today, more than anytime in gynecologic surgery, there are myriad techniques of performing uterine-conserving myomectomy procedures and hysterectomy:
 - Traditional laparotomy
 - Vaginal
 - Laparoscopic
 - Robotic
 - Hysteroscopic
- How durable are the procedures?
- Can the ideal patient be identified?
- For uterine-conserving procedures, how do procedures impact fertility, pregnancy outcomes, and recurrence?

Critical Gaps in Evidence

- Sexuality after hysterectomy
- Does removal or retention of the cervix affect orgasm?
- Is there a difference in sexuality following myomectomy or hysterectomy?

Potential New Research Areas

- Most research on novel surgical approaches has short-term data and follow-up
- Generally, surgical studies address surgical time, complications, length of hospital stay, and uterine volume
- Prospective long-term registries and validated questionnaires that follow women for one to five years after surgery are critical to access durability and pregnancy related outcomes
- This information is lacking and would affect counseling and recommendations for women

Critical Gaps in Evidence

- Without doubt, the uterus/cervix/vagina are monumental female organs that affect pregnancy and female sexuality/pleasure
- A paucity of short-term and long-term data exists to counsel patients about the potential benefits, harms, or long-term sexual function consequences of hysterectomy
- Gynecologists having quality data could counsel more effectively on whether cervical preservation makes a difference in sexual function

Potential New Research Area

Question #1:

How do uterine-conserving procedures impact fertility, pregnancy outcomes, and recurrence?

Justification for Question #1

| | |
|----------------|--|
| Question | <ul style="list-style-type: none">How do uterine-conserving procedures impact fertility, pregnancy outcomes, and recurrence? |
| Population | <ul style="list-style-type: none">Women who would like to retain their uteri for future pregnancy options |
| Research Need | <ul style="list-style-type: none">Currently, limited data to inform patients of answers to these questions |
| Proposed Study | |
| Timeline | <ul style="list-style-type: none">Patient commitment three to eight years |
| Cost | |

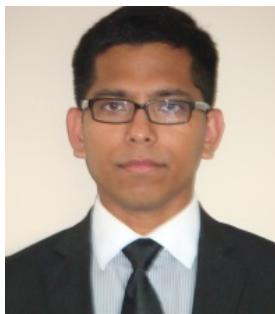
Potential New Research Area

Question #2:

Does removal or retention of the cervix affect sexual functioning? (dyspareunia or orgasm)

Justification for Question #2

| | |
|-----------------------|---|
| Question | <ul style="list-style-type: none">• Does removal or retention of the cervix affect sexual functioning? (dyspareunia or orgasm) |
| Population | <ul style="list-style-type: none">• Sexually active women (self or partner) who are having hysterectomy with/without cervical removal |
| Research Need | <ul style="list-style-type: none">• Are there potential benefits, qualitative changes in sexual function, harms, or long-term sexual function consequences to removal or retention of the cervix in women undergoing hysterectomy who have ovarian preservation |
| Proposed Study | <ul style="list-style-type: none">• Validated sexual function questionnaire completed three to six months prior to hysterectomy (with and without retention of cervix) |
| Timeline | <ul style="list-style-type: none">• Total enrollment period three to five years |
| Cost | |



Bijan J. Borah, PhD
Mayo Clinic

Elizabeth A. Stewart, MD
Mayo Clinic

Patient-Centered Outcomes Research Institute

Seimone Augustus: 26-Year-Old WNBA All-Star Forward



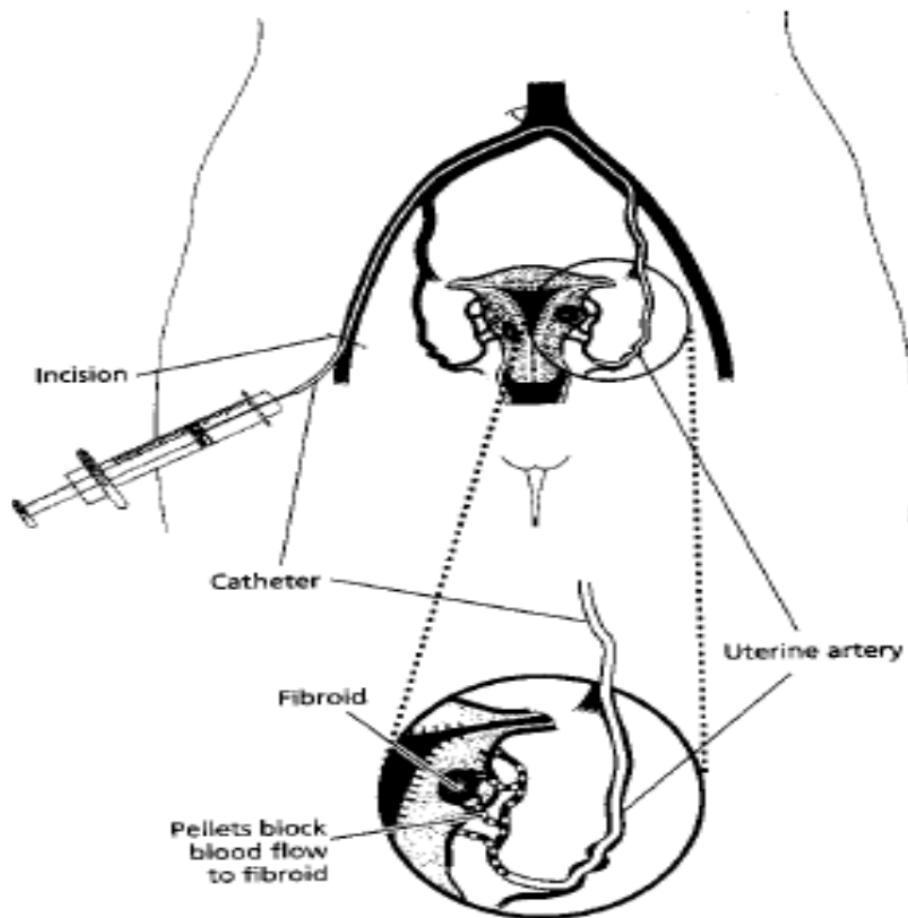
Associated Press
May 4, 2010

She had “three... fibroids removed ... 10 days ago... One of the fibroids was as big as a baby's head, and another was the size of a grapefruit... Her uterus needed to be taken out. Her ovaries were saved, so she can use a surrogate mother if she wants to have a baby in the future... Augustus said her mother and grandmother also had fibroids, and that a family friend died from complications during a similar surgery.”

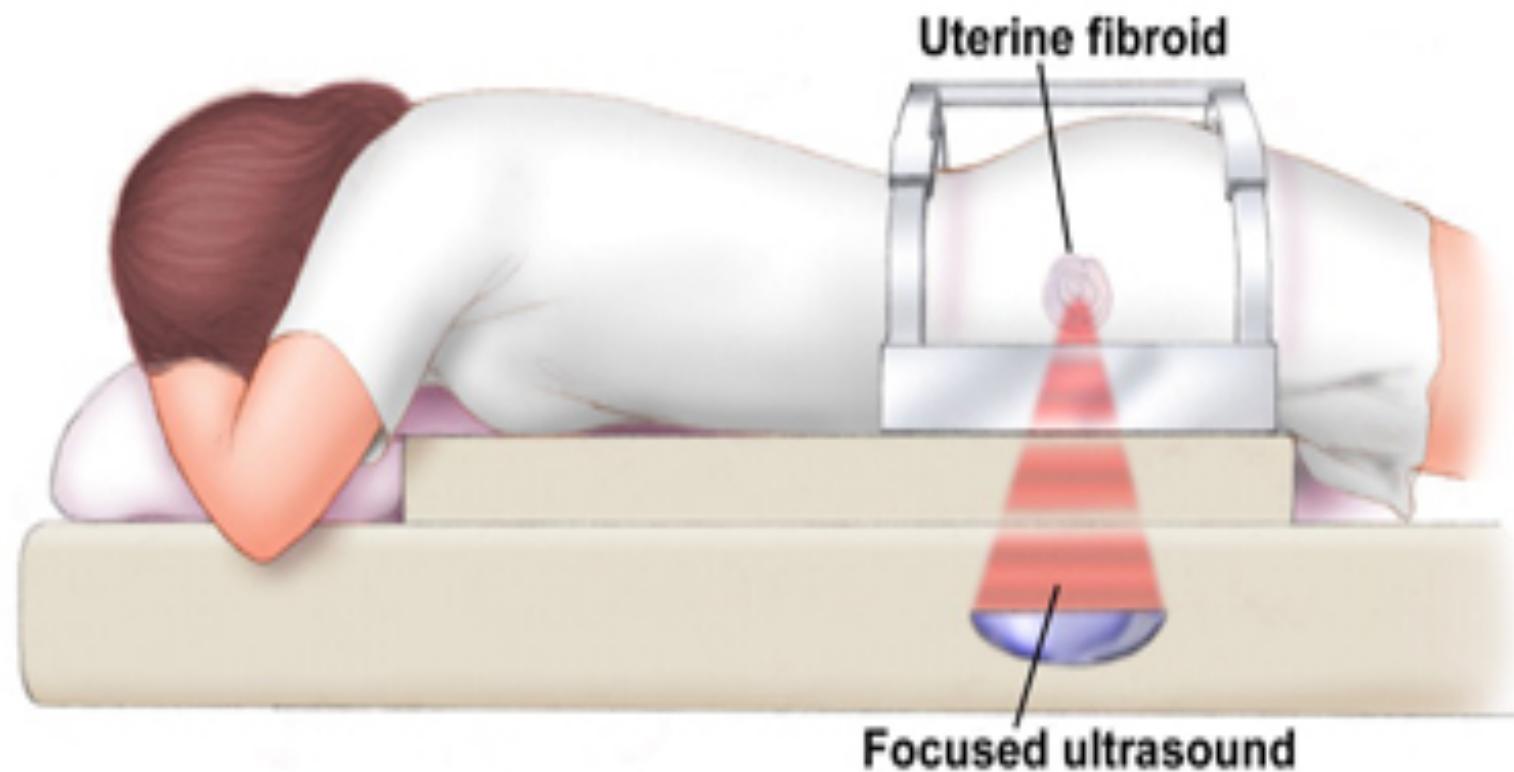
Why Fibroids?

- Women with fibroid symptoms are experiencing the peak demands of the “sandwich years”
- **Thus, they can advocate for their children with autism or their parents with Alzheimer’s, but do not advocate for themselves**

UAE or UFE: Stewart, E. A. *Uterine Fibroids*, 2007



MR-guided Focused Ultrasound Surgery



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GnRH-Agonists: “Maximal Short-term Efficacy”

- High probability of amenorrhea, addressing heavy menstrual bleeding
- Volume reduction addressing bulk symptoms
- Limited to six to 12 months of therapy due to hypoestrogenic side effects (e.g., hot flashes, bone density loss, etc.)
- Rapid rebound to baseline

Progesterone Receptor Modulators (PRMs) Compared to GnRH-agonists

- Similar control of bleeding, but faster onset
- Less volume reduction, but possibly longer carryover
- Few side effects and less estrogen suppression
- Current studies support efficacy for three months, but long-term endometrial safety needs to be addressed

Lifestyle Factors That May Be Associated With Uterine Fibroids

- Weight and BMI
- Physical activity
- Diet (soy, dairy, meat, fruit...)
- Vitamin D
- Stress

Limited Information of Alternative and Complementary Therapies

- Some published studies on traditional Chinese medicine
- Patients may use other therapies that are advocated on the Internet and not proven effective or safe

Hysterectomy with Ovarian Conservation: Our “Gold Standard” Is, at Best, “Gold-Plated”

- Increased CV risk when younger than 50 years old
- Earlier menopause
- Sexual dysfunction?
- Pelvic prolapse?

Ingelsson et al. Eur Heart J, 32:745-50, 2011
Farquhar et al. BJOG, 112:956-62, 2005
Moorman et al. Ob Gyn, 118:1271-9, 2011

Critical Gaps in Evidence

- What is the appropriate patient-centered efficacy endpoint for noninvasive fibroid therapies based on patient and disease factors? **Volume reduction?** **Decreased menstrual bleeding?** **Quality of life?**
- Is hysterectomy the appropriate patient-centered benchmark of therapy? **Is this an acceptable option for most women?** Are we underestimating long-term morbidity? **Hysterectomy versus minimally invasive therapy every three years?**

Critical Gaps in Evidence

- What is the appropriate time frame for intervention? Is there a “tipping point” for optimal intervention? Are there appropriate prevention strategies (e.g., lifestyle factors, diet)?
- What is the comparative effectiveness of appropriately timed and conceived noninvasive therapies?
- Are women more satisfied with the treatment outcome when they received care and counseling as part of an interdisciplinary team?

Potential New Research Area

Question #1:

What is the proper efficacy endpoint for noninvasive fibroid therapies based on patient and disease factors?

Justification for Question #1

| | |
|-----------------------|---|
| Question | <ul style="list-style-type: none">• What is the proper efficacy endpoint for noninvasive fibroid therapies based on patient and disease factors? |
| Population | <ul style="list-style-type: none">• All women seeking fibroid therapies |
| Research Need | <ul style="list-style-type: none">• Current Rx compared to hysterectomy• Variable guidance with FDA approvals• Cost-effective, but may not be patient-centered• Short-time horizon, usually six to 12 months; always less than five years |
| Proposed Study | <ul style="list-style-type: none">• Community engaged research approach that involves triangulate data• Potential study population:<ul style="list-style-type: none">▪ Women desiring childbirth or not▪ Comparison across a variety of sociodemographic characteristics (i.e., black vs. white vs. Hispanic vs. Asian) |
| Timeline | <ul style="list-style-type: none">• Two to three years, depending on the size and geographic spread of the study |
| Cost | <ul style="list-style-type: none">• Depends on the size of the study, but will be easily over \$500K |

Potential New Research Area

Question #2:

Is hysterectomy the appropriate patient-centered benchmark of therapy?

Justification for Question #2

| | |
|-----------------------|---|
| Question | <ul style="list-style-type: none">• Is hysterectomy the appropriate patient-centered benchmark of therapy? |
| Population | <ul style="list-style-type: none">• Women seeking fibroid symptom relief, women 10 to 60 years post hysterectomy |
| Research Need | <ul style="list-style-type: none">• Cultural impact of hysterectomy• Cultural impact of sexual dysfunction• Long-term morbidity of hysterectomy |
| Proposed Study | <ul style="list-style-type: none">• Community engaged research approach that involves triangulate data• Potential study population:<ul style="list-style-type: none">▪ Women desiring childbirth or not▪ Comparison across a variety of sociodemographic characteristics (i.e., black vs. white vs. Hispanic vs. Asian) |
| Timeline | <ul style="list-style-type: none">• Two to three years |
| Cost | <ul style="list-style-type: none">• Depends on the size of the study |

Potential New Research Area

Question #3:

What is the appropriate time frame
for intervention?

Justification for Question #3

| | |
|-----------------------|---|
| Question | <ul style="list-style-type: none">• When should intervention occur? |
| Population | <ul style="list-style-type: none">• All women seeking fibroid therapies |
| Research Need | <ul style="list-style-type: none">• When asked to live with symptoms until intervention is “appropriate”?• Since UF is chronic disease, is it preferable to have multiple minor interventions to one major intervention? |
| Proposed Study | <ul style="list-style-type: none">• RCT• Potentially a retrospective cohort study• Need for registry |
| Timeline | <ul style="list-style-type: none">• Two to three years (retrospective component only); RCT longer than three years |
| Cost | <ul style="list-style-type: none">• Depends on the study design |

Potential New Research Area

Question #4:

What is the comparative effectiveness of appropriately timed and conceived noninvasive therapies?

Justification for Question #4

| | |
|-----------------------|---|
| Question | <ul style="list-style-type: none">• What is the comparative effectiveness of appropriately timed and conceived noninvasive therapies? |
| Population | <ul style="list-style-type: none">• All women seeking fibroid therapies |
| Research Need | <ul style="list-style-type: none">• Need short-term and long-term outcomes• Need to assess recurrence risk |
| Proposed Study | <ul style="list-style-type: none">• RCT with parallel enrollment with capture of confounders |
| Timeline | <ul style="list-style-type: none">• Exceeds PCORI time horizon |
| Cost | <ul style="list-style-type: none">• Exceeds PCORI budget; very expensive, especially because insurers do not cover new therapies |

Potential New Research Area

Question #5:

What role do lifestyle factors play?

Justification for Question #5

| | |
|-----------------------|--|
| Question | <ul style="list-style-type: none">• What role do lifestyle factors play? |
| Population | <ul style="list-style-type: none">• All women seeking fibroid therapies |
| Research Need | <ul style="list-style-type: none">• Enduring in nature• Minimally invasive interventions may have other health benefits |
| Proposed Study | <ul style="list-style-type: none">• RCT with parallel enrollment |
| Timeline | <ul style="list-style-type: none">• Longer than three years |
| Cost | <ul style="list-style-type: none">• Cost may exceed PCORI funding for small projects |

Potential New Research Area

Question #6:

Are women more satisfied with the treatment outcome when they receive counseling as part of an interdisciplinary team?

Justification for Question #6

| | |
|-----------------------|---|
| Question | <ul style="list-style-type: none">• What are the expected outcomes? Are women more satisfied with the treatment outcome when they receive counseling as part of an interdisciplinary team? |
| Population | <ul style="list-style-type: none">• All women seeking fibroid therapies |
| Research Need | <ul style="list-style-type: none">• Enduring• Develop patient-centered care guidelines |
| Proposed Study | <ul style="list-style-type: none">• Use community engaged research approach and triangulate data• Potential study population:<ul style="list-style-type: none">▪ Women desiring childbirth or not▪ Comparison across a variety of sociodemographic characteristics (i.e., black vs. white vs. Hispanic vs. Asian) |
| Timeline | <ul style="list-style-type: none">• Two to three years, depending on the size and geographic spread of the study |
| Cost | <ul style="list-style-type: none">• Depends on the size of the study, but will be easily over \$500K |

Potential New Research Area

Question #7:

How to choose the most appropriate treatment modalities (e.g., non-surgical options) that are suitable for my individual case? Situations?

Justification for Question #7

| | |
|-----------------------|---|
| Question | <ul style="list-style-type: none">• How to choose the most appropriate treatment modalities (e.g., non-surgical options) that are suitable for my individual case? Situations? |
| Population | <ul style="list-style-type: none">• All women seeking fibroid therapies |
| Research Need | <ul style="list-style-type: none">• This question needs to be addressed after the effectiveness of various interventions are well-established• Develop patient-centered care guidelines |
| Proposed Study | <ul style="list-style-type: none">• Use community engaged research approach and triangulate data• Potential study population:<ul style="list-style-type: none">▪ Women desiring childbirth or not▪ Comparison across a variety of sociodemographic characteristics (i.e., black vs. white vs. Hispanic vs. Asian) |
| Timeline | <ul style="list-style-type: none">• Two to three years, depending on the size and geographic spread of the study |
| Cost | <ul style="list-style-type: none">• Depends on the size of the study, but will be easily over \$500K |

Progress in Medicine: The Roadmap for Fibroids

- Predictors of prognosis
- Comparison of available treatment options
- Optimized therapy
- Early intervention
- Secondary prevention
- Primary prevention



Patient and Stakeholder Perspectives on Information Gaps

Patient-Centered Outcomes Research Institute



Comments from Public

Patient-Centered Outcomes Research Institute

How to Provide Comments Today

- Email (fibroids@pcori.org)
- Twitter (hashtag #PCORI)
- The webinar “chat” feature
- The “Submit a Question on our Targeted Topics” page on our website
- By telephone. Our operator will now tell you how to let us know if you have a question or comment.



Lunch Break

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Discussion of Critical Gaps in Fibroids Research and Key Research Questions

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Criteria for Knowledge and Research Gaps

- Knowledge gaps should:

- **Be patient-centered:** Is the proposed knowledge gap of specific interest to patients, their caregivers, and clinicians?
- **Assess current options:** What current guidance is available on the topic and is there ongoing research? How does this help determine whether further research is valuable?
- **Have potential to improve care and patient-centered outcomes:** Would new knowledge generated by research be likely to have an impact in practice?
- **Provide knowledge that is durable:** Would new knowledge on this topic remain current for several years, or would it be rendered obsolete quickly by subsequent studies?
- **Compare among options:** Which of two or more options lead to better outcomes for particular groups of patients?



15 Minute Break

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Continued Discussion of Critical Gaps in Fibroids Research and Key Research Questions

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Criteria for Knowledge and Research Gaps

- Knowledge gaps should:

- **Be patient-centered:** Is the proposed knowledge gap of specific interest to patients, their caregivers, and clinicians?
- **Assess current options:** What current guidance is available on the topic and is there ongoing research? How does this help determine whether further research is valuable?
- **Have potential to improve care and patient-centered outcomes:** Would new knowledge generated by research be likely to have an impact in practice?
- **Provide knowledge that is durable:** Would new knowledge on this topic remain current for several years, or would it be rendered obsolete quickly by subsequent studies?
- **Compare among options:** Which of two or more options lead to better outcomes for particular groups of patients?



Recap and Next Steps

Patient-Centered Outcomes Research Institute

We Still Want to Hear From You

- We welcome your input on today's discussions or our process in general
- We're accepting comments and questions for consideration on this topic through 5 pm ET March 19th via:
 - Email (fibroids@pcori.org)
 - Our "Submit a Question on our Targeted Topics for Research Funding" web page
- We'll take all feedback into consideration

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**Thank You for Your
Participation**

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