Innovation through the Lens of Women’s Health Research: A rising tide lifts all boats!

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Virtual (from Cambridge, MA)
Endometriosis: A Chronic Inflammatory Disease

Ectopic Growth of endometrium (glands & stroma)

- Affects ~10% of women
- Causes debilitating pain, infertility, anemia
- Onset often in teens, 7-10 years to diagnosis
- Surgery is required for diagnosis

**Treatments**

- oral contraceptives
- Lupron
- aromatase inhibitors
- danazol
- surgery (surgery, ....)


Giudice, *NEJM* 2010; Potlog-Nahari, *Fertility & Sterility* 2004
“The ‘typical’ patient with endometriosis will be a nulliparous patient in her late twenties or early thirties. Textbooks* describe her as intelligent, egocentric, overanxious, and a perfectionist”

* such as this one

...Or, (Severe) Diagnosis Bias?!
2006: My reaction when female Ob/Gyn tells my sister:
“Colonoscopy is negative –
Your daughter (age 15) is making things up to get out of going to school”

Actual diagnosis:
endometriosis (on bowel)
How far-reaching are the consequences of gaps in women’s health funding, for women & for all? (We need more data!)

1. How does the lack of effective diagnosis & treatments for common gynecological (& women’s health problems) affect general population health?

Healthy uterus / mom → healthy baby (toddler, teen, adult)
- Uterine & ovarian pathologies (heavy bleeding, fibroids, endometriosis, adenomyosis, Ashermann’s, polycystic ovarian, vulvodynia) afflict at least xx %* of teens and yy%* 20s & zz%* 30s
- Fertility research / treatment ≠ uterine health research/treatment!

*estimates are >25%

2. Over 500,000 hysterectomies per year in US (1/3 of all women by age 60)
- Hysterectomy associated with known increases in risk of heart disease, other illnesses (possibly due to poor management of diseases leading to hysterectomy?)
- Are all the health consequences really known? (Eg. insomnia leading to reduced immune function, increased infections, etc).
How far-reaching are the consequences of gaps in women’s health funding? (We need more data!)

How much does cumulative excess morbidity of gynecology & female-skewed diseases contribute to the “women’s pay gap”?

- Gynecology & female-skewed diseases are chronic, with lack of adequate treatments and high morbidity in productive life years
- Although relatively understudied, published data suggest women miss more work than men, because they themselves are sick (i.e., not just caregiver role)
- Large, well-controlled economic studies in US are missing. We desperately need them!

The herd of elephants in the room affecting women @ work

See eg. work of Emily Oster @ Brown
Gynecology* appears very underfunded – more analysis needed!

*Infertility, pregnancy ≠ gynecology

Huge gaps in this analysis!
Because of huge gaps in NIH data and funding!

**Example:** Adenomyosis funding not represented

- There is no RCDC category, despite prevalence ~ endometriosis
- only 2 grants (both R01s) in the entire NIH Reporter
  - 2002-2006, NICHD (Epidemiology)
  - 2021 – continuing, NICHD (Basic science)
- DALYs are unknown – prevalence is ~ 10-fold underestimated
- NIH Reporter cites “89” projects – misleading!
  - only 2 are actually adenomyosis-focused
  - others mention adenomyosis incidentally

Plot by Ron Chandler, MSU, of data from Mirin, J. Women’s Health, 2021
Gynecology/ Women’s Health funding is relatively unstable—unusually high reliance on special programs for major grants

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- **Unsolicited (“investigator initiated”) proposals**
  - Investigator/team develops proposal idea
  - Three known submission deadlines per year, every year, allows investigators to submit when ready
  - Unsuccessful proposals can be re-submitted 2x, answering comments from reviewers
  - Investigators can seek NIH Program Manager feedback for improving proposal aims and impact before submission; this may be especially helpful to Early Stage Investigators

- **Solicited “Funding Opportunity Announcement” proposals**
  - NIH Program managers hold workshops, develop criteria, seek internal review and approval for FOA
  - Timing of public announcement is “whenever” (admin approval)
  - Investigators must write a grant that is “responsive” to the FOA criteria, typically within 8-10 weeks of FOA posting
  - Set-aside budget regardless of how many well-scored proposals
  - One-time submission; no revisions

Data compiled by Elizabeth Barr, NIH ORWH, from RCDC queries

Acknowledgements: Pierre Azoulay (MIT Sloan); Rem Koning (Harvard Business School)
How might unusually high reliance on special programs impair research on gynecology/women’s health? (review process)

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• Unsolicited (“investigator initiated”) proposals are reviewed by “Standing Study Sections” – promotes robust community
  - Stable cadre of reviewers who meet 3X per year (4-year terms)
  - Expertise of reviewers vetted by a nomination process
  - Additional reviewer vetting by ad hoc service before selection
  - Investigators submit when ready, can revise/resubmit
  - Proposal feedback provided by calibration against the arc of the field, helps young investigators, program managers can provide one-on-one feedback to improve proposals

• Solicited (“Funding Opportunity Announcement/FOA”) proposals are reviewed by ad hoc “Special Emphasis Panels”
  - Reviewers recruited for 1-time panel
  - Experienced reviewers / investigators are often conflicted by submission of proposals to FOA
  - No resubmission
  - no competing continuation of funded grants (one-off)

Fields funded heavily by FOAs are at a disadvantage for building a robust research community

Acknowledgements: Pierre Azoulay (MIT Sloan); Rem Koning (Harvard Business School)
Outside analysis a must for this multi-faceted problem

Lack of dedicated funding for gynecology
- no “Institute for Reproductive Health”
- most funding is through “Child Health and Development”, which has many competing research areas
  - What’s in a name....??!!

Lack of experienced reviewers on standing study sections, broadly
- low “significance” scores for gynecology?
- Gynecology too complex ??

Lack of appropriate / accessible collaborative funding modes
- Many gynecology conditions are co-morbid

Need outside expert analysis of the entire application & funding process
- Follow examples of outside analysis of confidential Census, IRS, EEOC, etc. data by scholars from NBER and NORC through creation of data enclaves (analyses themselves may be $0 cost to NIH, funded by NSF, etc)
- Key to data sharing agreements is that DATA are shared, not just outcomes (e.g. – who applied; what was actually in the application; confidential reviewer score data; were there hugely discordant scores etc.)
- How does expertise and bias play into proposal review (see e.g. work by Danielle Li, MIT Sloan)
- How might new modes of funding (eg through defined collaborative efforts) shift new investigators into gynecology/women’s health (see e.g. work by Kyle Myers, Harvard Business School)

Acknowledgements: Pierre Azoulay (MIT Sloan); Rem Koning (Harvard Business School)
Artificial Intelligence (AI): *Innovation Embraced in Medicine*

**Predicting Future Cancer**

Breast cancer care and research is relatively well-funded.

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AI/ Machine Learning Are Effective when:

- Images or (well-curated) data exist

- Questions are well-posed to match the data

Most therapeutic *treatment* and *development* lies outside this realm

**ESPECIALLY** in Gynecology & Women’s Health
AI & Adenomyosis?

---|---|---
Crohn’s/UC | ~1% | 60,237
Adenomyosis | 2-5%? | 3,115

Evan Chiswick, Keith Isaacson, Tony Guidi, Ed Boyden/lab, Linda Griffith, unpublished
AI & Adenomyosis Diagnosis / Prognosis?

Difficult/impossible to “innovate” with current lack of infrastructure for basic studies...

With 500,000+ hysterectomies a year, we SHOULD be able to build the infrastructure for image-guided diagnosis!!

We SHOULD be able to build evidence-based infrastructure for biopsies on non-hysterectomy patients!

No $$ for infrastructure thus far.

No feasible biopsy process to correlate with all images yet exists

• Very difficult to “hit” lesion in hysteroscopic OR laparoscopic biopsy – clues in the adjacent myometrium?

AI & Adenomyosis - Therapy development?
*Genomic insights are only the tip of the iceberg

Caution: targeted drug discovery should not be disconnected from mechanistic understanding of dynamic signaling networks
AI/Genomics Analysis gives clues, not (yet) answers....

*example for adenomyosis sister disease, endometriosis*

**Genetic Linkage Study (Endometriosis), 32 families**

Common variants observed in 11% European women

Tapmeier...Zondervan, Sci Trans Med, August 2021

*Neuropeptide S Receptor 1 is a Non-hormonal Treatment Target in Endometriosis*
Endometriosis/adenomyosis is not one disease – one drug (class) does not fit all!

Patient Heterogeneity
- age of onset
- symptoms
- immune system
- drug response
- co-morbidities

Lesion Heterogeneity, between/within patient(s)
- biology - glandular, fibrotic EMT, etc
- physiology – drug access?
- one drug for all lesions?

Molecular mechanistic stratification is needed!

Becker +, WERF EPHect Working Group
Harmonization Project I, Fert & Stert (2014)
Hypotheses

- Patients can be grouped and treated according to different molecular mechanisms of disease (similar to cancer)

- Molecular mechanisms may correlate (or not) with symptoms rather than lesion burden

How do we find the mechanisms and groups?
Engineering Approach

**Inflammation / Invasion PATHWAYS are Linked into Complex NETWORKS:**
Cell-Cell Signaling Proteins (cytokines, chemokines, growth factors), Enzymes (proteases, kinases) etc.

Mechanism-based Molecular Classification of Endometriosis Patients

Identification of JNK as a new non-hormonal target in a subset of patients

Funded by an Anonymous Foundation (not NIH)

All (77) Patients (Stage I-IV) compared to Controls (20)

Consensus Signature
1/3 of patients, all disease stages

Jun kinase regulates inflammatory cytokine production

Peritoneal Fluid

50-plex Luminex of cytokines

Multivariate Unsupervised Analysis

Reverse engineer immune network, test hypothesis in patient macrophages

Replicated in a meta-study with Mauricio Abrão et al, São Paulo (in prep)
What are the consequences of inflammation on invasion of ectopic endometrial cells into underlying tissue? *Jnk also implicated*

Resection of 2 bowel endometriosis lesions + associated other endometriosis, Dr. Mauricio Abrão, Sirio Libanês Hospital 12 July 2011

Miller *et al*, *Integrative Biology* (2011)
Miller *et al*, *PNAS* (2012)
JNK inhibitors have cured diverse patient populations of endometriosis!

*(unfortunately, none are human)*

Clinical trial of JNKi (Preglem) unsuccessful – Patient stratification issue? Drug chemistry/specificity?

*Pharma: “we need efficacy models”*
Modeling the Birth of Lesions With Tissue Engineering & Organs on Chips

Synthetic matrix/tissue engineering/Organ-on-chips supported by foundations and DARPA 2012 – 2017 then NIH 2019+ -

Endometrial Gland in Culture

Recruitment of circulating (immune/stem) cells
Ellen Kan with Roger Kamm lab

Microvascular networks driven by gravity flow in a commercial chip

Human Monocytes (Cell Tracker)
HUVEC (UEA-1)

*real time
Example of Women’s health need driving innovation for all: Human on a chip – with protocols for sex dimorphism analysis

We MUST move beyond animal models – especially for chronic inflammatory diseases

**Standard PDMS “Organ on Chip”**
Wyss Institute (Ingber)

Sink for estradiol - cannot use for sex dimorphism!

**V2.0 Hard Plastic: Endometriosis on a Chip**
MIT (Griffith + Trumper)

NIH Tissue Chips Program 2019+

True microvasculature and control of estradiol/progesterone/testosterone!

**Version 1.0 Hard Plastic, open system liver**
MIT/Griffith-Trumper/CN BioInnovations

DARPA Microphysiological Systems Program 2012-2019
The Emergence of “Biological Engineering” as a Model for a New Era of Trans-NIH collaboration

(Bio) Medical Engineering: Applications

Mechanical, electrical, materials engineering, etc applied to medical problems
No particular need to know Biology, probably knows some physiology

Biological Engineering: a New Engineering Discipline

Engineering Analysis, Design, and Synthesis - based in Modern Molecular Life Science
Emphasis on Problem Definition! Must know biology
Not essential to know “instrumentation” or “fabrication”

Models tell you what to build
The Emergence of “Biological Engineering” as a Model for a New Era of Trans-NIH collaboration

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Bernard M. Gordon Prize for Innovation in Engineering Education
2021: Linda Griffith & Doug Lauffenburger, MIT

CITATION: For the establishment of a new biology-based engineering education, producing a new generation of leaders capable of addressing world problems with innovative biological technologies.
Biological Engineering As an Essential Discipline

Biological Engineering

Analysis
(uses math, physics, chemistry)

Synthesis

(Bio)Medical Engineering

medicine

candidate area(s)

BE

BE ChE MSE ME EE CS

biology chemistry physics

math

substrate science(s)

biology (molecular to ‘omic)
Biological Engineering emerged organically over ~10 years

**School of Engineering**
- AeroAstro
- Chemical
- Civil & Environmental
- Electrical & Comp. Sci
- Materials
- Mechanical
- Nuclear
- Ocean

**1985-2005**
- NSF “Biotech Process Engineering Center”
  - Research, co-taught elective subjects

**1993**
- Ad hoc inter-departmental UG BioEng Curriculum Committee formed: Should MIT have a “Biomedical Engineering” Major?

**1993 Biomedical Eng.Minor Degree**
- Biology required for all students
- MIT’s 1st interdepartmental Minor Degree
- Requires: Biochem, Genetics, Cell Bio

**1994**
- Formal pan-MIT grass roots faculty proposal to start a program “linking engineering to molecular life science @ MIT; MIT Admin says “yes”

**1998 The Big Academic Experiment**
- “Division of Bioengineering & Environmental Health” launches in School of Engineering
- 6 faculty split appointments 50/50 with ChE, ME, EECS, etc; 11 Toxicology faculty move to “BEEH”

**1999**
- PhD in “Biological Engineering” launched
- 80+ students enrolled in BME Minor
- >25% are Biology majors

**Whitaker College**
- Health Sci & Technology
  - (Medical Engineering Graduate Education)

**Harvard Medical School MD programs**
Biological Engineering emerged organically over ~10 years

**Ca. 2000**

- **School of Engineering**
  - AeroAstro
  - Biological
  - Chemical
  - Civil & Environmental
  - Electrical & Comp. Sci
  - Materials
  - Mechanical
  - Nuclear
  - Ocean

**2000**

- UG Committee begins developing curriculum for major in “Biol Eng.”
- Emphasis on teaching collaborations between departments / schools

**2001**

- Name change to “Biological Engineering (BE) Division”

**2002**

- “BE Division” becomes permanent academic unit after formal MIT review

**2003**

- “BE Division” becomes “BE Department”, on par with all SoE Departments
- Biological Physical Chemistry launched
- Molecular Thermo/Stat mech collaboration between ME & BE

**2004**

- BE becomes “Course 20”

**2005 Biological Engineering UG Major**

- First new UG major in 39 years

**2007 Biol Dept joins “Biol P Chem”**

- Biol Prof volunteered when Griffith had emergency endometriosis surgery

**2005 Chem Dept joins “Biol P Chem”**

- Dean of Science Bob Silbey (Author of “Physical Chem, 4th Ed”) + Moungi Bawendi

- *Moungi and Linda started Lumicell + Precision Healing together (with others)*

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**School of Science**

- Brain and Cognitive Sci.
- Biology
- Chemistry
- Math
- Physics

**Whitaker College**

- Health Sci & Technology
  - (Biomedical Engineering Graduate Education)

- Harvard Medical School MD programs
Gradual emergence of a now-established discipline

**Years 1 and 2**
- **Physics (2 semesters)**
- **Calculus (2 semesters)**
- Biology
- Chemistry
- **MIT requirement**
- **BE requirement**
- **BE core**
  - Differential equations
  - Programming and statistics
  - Organic chemistry
  - Biochemistry
  - Thermo of Biomolecular Systems
  - Intro to Biol. Eng. Careers
  - *Biological Eng lab (wet)*

**Year 3**
- Genetics
- Cell biology
- Analysis of biomolecular and cellular systems
- Fields forces and flows in biol. systems
- *BioEng lab (instrumentation)*

**Year 4**
- Senior design
- (Thesis)
- + 3 Restricted Electives
Urgent Need for Workforce Development in Gynecology

• Research and teaching go hand in hand – top researchers usually want to teach (same for top clinical practitioners)

• Lack of robust clinician-scientist research culture in gynecology filters into difficulty creating evidence-based practice guidelines

• *Tremendous* interest in gynecology research from young women in STEM – *when they ask, I have no good advice for them about funding*

• I feel hesitant to encourage young scientists to study gynecology, due to uncertainties in funding
How Addressing Women’s Health “Raises All Boats”
Structural Changes to Improve NIH collaboration for All

- **The need:** extensive collaboration across ICs to address systemic and co-morbid conditions in women, from childhood through menopause with far more resources than are now available
- **The need:** better dissemination of “biological engineering” concepts across NIH
- **The challenge:** Difficult to build collaborative projects across ICs as each IC has its own budget and agenda – is “tin-cupping” a sustainable plan for gynecology?
- **The potential:** staff throughout NIH see potential for collaboration
- **The suggestion:** Pilot a new mode of NIH collaboration with a Gynecology Center (or other means of dedicated funding for Gynecology) in NICHD
- **The caution:** An Institute should take the lead – not the Office of the Director or ORWH
Gynecology as an example of Women’s Health Research that Desperately Needs A Quantum Change in Inter-IC Collaboration

**Example of Endometriosis / Adenomyosis**

- Chronic pain / quantitative metrics
- “brain fog” during drug treatment & menopause

- GI co-morbidity in peri-menarchal girls developing dysmenorrhea ultimately endometriosis
- Prevention of kidney disease precipitated by treatment for gynecological disease

**NICHD**
- Fetal-maternal medicine
- Fertility
- Rehabilitation
- Child health development

**NINDS**
- Correlation with cardiovascular disease – genetic predisposition or drug treatment?

**NIDDK**

**NHLBI**
Gynecology as an example of Women’s Health Research that Can Potentially Benefit Broad Areas of Human Health

Better understanding of Normal and Pathological Menstruation Processes

- Sex hormone regulation of migraine
- Chronic pain

- Immunology of mucosal barriers
- Stem cell dynamics and plasticity in mucosal barriers

**NHLBI**
- Sex hormone regulation of vascular properties
- Endometrial vasculature dynamics as a model system for development and study of cardiovascular disease
- Neuroangiogenesis in health and disease

**NICHHD**
- Fetal-maternal medicine
- Fertility
- Rehabilitation

**NINDS**

**NIDDK**
An Experiment – Gynecology as a new Collaborative NIH Model a la MIT Biological Engineering

Key Elements:

- Substantial dedicated, protected funding for Gynecology within NICHD
- Substantial funding toward defined ways other ICs collaborate with Gynecology

Careful analysis needed to avoid downsides of the Law of Unintended Consequences

Pilot experiment with 2-3 institutes, small budget % to determine best operational model

* Includes e.g. child-to-adult cohort studies

(≈2%) budget to collaboration grants with Gyn. Center
- Emphasize investigator – initiated
- Basic science and translational science
- Include studies on younger patients (pre-teens even) with co-morbidities requiring collaboration across disciplines
- TRAINING PROGRAMS / WORKFORCE DEVELOPMENT
Summary of recommendations

- Desperate need for outside analysis of funding disparities in Women’s Health, especially in gynecology but also infectious disease, etc.
- Desperate need for better data on how women’s health disparities influence wage gap for women (almost no studies exist for US!)
- NIH should encourage creation of an enclave allowing professionals from NBER, NORC, etc to analyze NIH data critically
- Women’s health – often difficult to approach from genomic analysis -- motivates new “biological engineering” approaches to chronic diseases, benefitting all
- Gynecology offers a roadmap to an experiment for new models trans-NIH collaboration in research and workforce development
- Dedicated funding to Gynecology, and ”Gynecology Collaboration”, should be within an Institute and not in the OD
- Outside analysis of how to set up dedicated funding & a collaborative model is encouraged