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American Medical Association Journal of Ethics

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FROM THE EDITOR

Advances in Gynecologic Oncology

During my fourth year of medical school, after deciding that I would pursue obstetrics and gynecology as a career, I had the opportunity to spend four weeks on the service of a busy gynecologic oncology service at a tertiary women's hospital. During those four weeks I developed an interest in this subspecialty of ob-gyn and came to appreciate the interactions between its practitioners and patients that so often played out against a backdrop of deeply personal and ethical dilemmas. The malignancies treated in the field of gynecologic oncology tend to affect those who are diagnosed in profound ways. These cancers are often aggressive, recurrent, and incurable. They often occur in young women, and treatments can carry with them radical surgeries and a burden of side effects that can alter the remainder of the women's lives. Together, these forces create high-stakes, emotional, and stressful physician-patient interactions that, I believe, deserve a journal issue all their own.

I am extremely excited about the contributions to this issue. In the case scenarios, our expert commentators tackle dilemmas specific to the field: fertility preservation for adolescent girls receiving treatment for gynecologic cancer and patient confidentiality about an inherited increase in risk of breast cancer.

One contribution to this issue, from a pioneer in the field of gynecologic oncology, chronicles the events that led to the realization that a drug widely prescribed to prevent pregnancy loss caused cancer in the offspring born from those pregnancies and considers how we can learn from this unfortunate event. We then look to the future. This is an exciting time in gynecologic oncology; for example, we now have a vaccine for human papillomavirus that could potentially eradicate a cancer that was once the leading cause of cancer deaths among women worldwide. Why, then, as one article discusses, are there barriers to more widespread use of the vaccine? Additionally, as research efforts to fine-tune chemotherapeutic agents and regimens to fight gynecologic cancers continue, equipoise in study designs is a constant consideration. Another piece examines the importance of the equipoise principle to the field and questions whether it is ethical to assign some research participants less-effective treatments to clearly demonstrate a new treatment's effectiveness, thereby making it more widely accessible to future patients.

As we continue to shed light on the etiologies of female cancers, we develop new treatments. With the newfound evidence that the fallopian tubes are an etiological epicenter for ovarian cancer, some have proposed prophylactic salpingectomies for

women at a higher risk for developing this type of malignancy. Another contribution offers valuable background on this technique, examines the guidance of the American College of Obstetricians and Gynecologists, and communicates some experiences and thoughts on the future of surgical prophylaxis for ovarian cancer.

The thought of death is not easy to grapple with. As mentioned before, female cancers can be quite aggressive and often recur. Because of this reality, end-of-life discussions are particularly frequent in this field and sometimes involve people who are facing their mortality prematurely. In this month's podcast, we feature an interview with a palliative care specialist at a large women's hospital who participates in these discussions with patients on a daily basis and offers ideas to help physicians, nurses, and other care team members conduct these most difficult conversations. This issue also includes a literary analysis of the 1999 Pulitzer Prize-winning play *Wit*, arguing that the play depicts parallels between scholarly literary exegesis and the practice of medicine. These two pieces set the stage nicely for a contribution about the implementation and necessity of a formalized ethics curriculum during the ob-gyn residency.

I am delighted that all of these pieces will be together in one issue that focuses on the field of gynecologic oncology. However, I am even more excited that this issue sheds light on the patients who are at the center of these discussions. As a profession, we often focus on how we can improve our skill set, how we can become better. Sometimes, though, we must focus on understanding the human condition and the circumstances of the patients who stand before us. Through understanding the patient experience, we can be more effective practitioners. I hope that the pieces offered by this month's contributors further the understanding of ethical issues in gynecologic oncology, facilitate meaningful conversation and debate among its practitioners and students, and, finally, help us all understand the experience of the patients affected by these malignancies.

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ETHICS CASE

Disclosing Information about the Risk of Inherited Disease

Commentary by Clint Parker, MD, PhD

Mrs. Durham was diagnosed with an invasive epithelial ovarian cancer and, in conjunction with conversations about her treatment, was offered genetic testing for the BRCA1 and BRCA2 mutations. It was revealed that she carried a harmful BRCA1 mutation that is known to increase the lifetime risk of breast and ovarian cancer significantly. Once the results came back, her oncologist brought up the option of a prophylactic mastectomy and advised her to inform her living relatives of the results of the test.

Mrs. Durham's primary care physician, Dr. Bartlett, expected she would do so, too. At her first appointment after the diagnosis, Dr. Bartlett asked Mrs. Durham how she was holding up and how her sister, Mrs. Weir—her only living family member and also one of Dr. Bartlett's patients—had taken the news.

"Oh. Well, I haven't told her."

"Are you going to?" asked Dr. Bartlett.

Mrs. Durham responded, "You know we haven't spoken in quite some time, and I can't imagine making this the topic of our first conversation."

"Yes, I know…but I think this is important information that may affect her health."

Mrs. Durham sighed. "We're estranged, for one thing, and for another, I want to keep my cancer private. I don't want people knowing I'm sick and pitying me."

Dr. Bartlett felt pulled in two directions—his obligation to respect Mrs. Durham's wishes and protect her privacy conflicted with his obligation to promote Mrs. Weir's health. BRCA1 mutations are not "reportable" illnesses like HIV and tuberculosis, so he was not compelled by law to break Mrs. Durham's confidentiality. Dr. Bartlett considered how he might be able to encourage Mrs. Durham's sister to be tested for the BRCA mutations while preserving Mrs. Durham's confidentiality.

Commentary

In our case, Dr. Bartlett appears to have a professional obligation to keep Mrs. Durham's private medical information confidential. He also appears to have an obligation to prevent harm to Mrs. Durham's sister, Mrs. Weir, who is also his patient. Because her sister has the BRCA1 mutation, there is an increased likelihood of Mrs. Weir's also carrying it, and, if she does, there is increased risk of harm from breast and ovarian cancer that could be reduced through prophylactic operations and aggressive screening. Therefore, Dr. Bartlett appears to have an obligation to counsel Mrs. Weir about her possible increased risk of cancer, about diagnostic testing that could verify whether she actually has this increased risk, and, if she does have the mutation and the concomitant increased risk of cancer that comes with it, about the therapeutic options available to her to decrease this risk.

On the face of it, it seems that Dr. Bartlett is confronted with an ethical dilemma. A true ethical dilemma involves competing moral obligations that cannot both be fulfilled and may take the following form: *Person A has a moral obligation to do act X and act Y, but cannot do both X and Y simultaneously*. In our case it seems that Dr. Bartlett must either protect Mrs. Durham's confidentiality or break this confidence to try to decrease the risk of a bad outcome for her sister.

Whether one considers ethical dilemmas real depends on what ethical theory one accepts. Some ethical theories are structurally monistic, that is, they assert that any moral choice can, in theory, be adjudicated by one overarching moral rule and that what appears to be a dilemma is not. Act consequentialism is a theory that functions in this way [1]: the right action in any given case is that act which, among the possible acts an agent could pursue, would bring about the best balance of good over bad consequences—however one defines good or bad consequences.

Most approaches to moral decision making in modern bioethics, however, are not monistic. Rather, it is common in modern bioethics to assume a pluralistic framework—one in which multiple, competing moral claims do not simply reduce to an overarching moral claim [2, 3]. Unlike in monistic systems, in some pluralistic systems, moral dilemmas can arise [4].

In pluralistic systems, there are at least three different ways of thinking about conflicts between moral claims. First, one can take an optimistic view and hold that as long as one fulfills at least one of the competing moral obligations, one has acted rightly. So, as long as Dr. Bartlett *either* keeps Mrs. Durham's information confidential *or* breaks confidentiality for the good reason of counseling her sister regarding her possible increased risk of cancer, he has done what is right. Alternatively, one can take a pessimistic view and hold that as long as one has failed to fulfill one of the competing moral obligations, one has acted wrongly. This would present a true ethical dilemma;

regardless of whether Dr. Bartlett keeps Mrs. Durham's medical information confidential or breaks confidentiality in order to counsel her sister, he has acted wrongly. However, there is a third way to think about conflicts between competing moral claims that does not assume each moral consideration to be an *actual* moral obligation.

In this third approach, individual moral considerations, each of which is considered to have some degree of moral force when viewed in isolation, are called *prima facie* moral obligations [5]. The job of the moral agent is to balance the competing *prima facie* moral obligations and come up with an *all-things-considered* (ATC) judgment about what to do in a given case. *Prima facie* obligations can be thought of as wrong-making or right-making properties. For example, the act "Dr. Bartlett divulges Mrs. Durham's confidential information" can fall under different act descriptions. It can be described as an act of "breaking confidentiality," and it can also be described as an act of "preventing harm." Thus the same act has two moral properties—the wrong-making property of violating a *prima facie* obligation to maintain patient confidentiality and the right-making property of fulfilling a *prima facie* obligation to prevent harm.

The ATC judgment is an intuitive act of moral reasoning in which we consider *all* of the right- and wrong-making properties of the act and then judge whether the act is actually wrong, morally required, or permissible. It is this judgment that is ultimately action guiding, and it is these properties (i.e., wrongness or obligatoriness) that ultimately provide warrant for moral attitudes such as blame and praise. On this view, *prima facie* obligations are not *actual* obligations and, therefore, cannot lead to a true ethical dilemma. That is, taken individually, they do not necessarily obligate us. They are ways of describing the right- and wrong-making properties of acts that then must be weighed against one another to determine whether the act is actually morally required or prohibited. We may use the term *obligation* in *prima facie* obligations because if there is only one morally relevant description of an act, then the *prima facie* obligation exemplified by that act description would determine the rightness or wrongness of the act, which would then actually obligate us.

For our case, I will adopt this third approach, and our task will be to see which of the possible actions available to us is the right thing to do, given our *prima facie* obligation to keep Mrs. Durham's private medical information confidential and our *prima facie* obligation to counsel Mrs. Weir in order to prevent possible harm.

Analysis of This Case

There are at least four different actions that Dr. Bartlett could take. First, he could simply not counsel Mrs. Weir regarding her possible increased risk of cancer. Second, he could break confidentiality, tell Mrs. Weir that Mrs. Durham tested positive for the BRCA1 mutation, counsel her regarding her own risk of carrying the mutation, and recommend getting tested. Third, he could try to convince Mrs. Durham to tell her sister about her

positive BRCA1 test or, at least, to give him permission to do so. Finally, Dr. Bartlett could simply advise Mrs. Weir that he believes that she is at risk for the BRCA1 mutation and should get tested for it. If she asks why, then he could inform her that, while he is not at liberty to disclose all of the details of *why* he believes she is at increased risk, he has come to that conclusion and would like for her to trust that he is acting in her best interest.

I will argue against the first two approaches and for a combination of the last two approaches. The main ethical consideration that supports counseling Mrs. Weir to get tested is that physicians have a *prima facie* obligation to try to prevent disease from harming their patients. By not counseling Mrs. Weir about her possible increased risk of the BRCA1 mutation, Dr. Bartlett would be depriving her of information she needs to make a decision about tests and procedures that might help reduce her risk of cancer. However, if Dr. Bartlett simply told Mrs. Weir that Mrs. Durham had cancer and tested positive for the BRCA1 mutation, then he would be violating the competing *prima facie* obligation to keep Mrs. Durham's medical information confidential.

Certainly, if Mrs. Durham told her sister herself or consented to allowing Dr. Bartlett to share this information with her sister, that would allow Dr. Bartlett to act in a way that did not violate patient confidentiality and would likewise allow him to fulfill his *prima facie* obligation to try to prevent harm to Mrs. Weir. It would be morally acceptable for Dr. Bartlett to have an open and honest discussion with Mrs. Durham about why he would want to share this information with her sister, offer a moral argument for why this would be appropriate, and make a direct recommendation such as, "I think you should allow me to share this information with your sister because it may help her make decisions that could decrease her risk of getting cancer."

Let's assume that, for whatever reason, Mrs. Durham again refuses. Whatever one may think about the moral propriety of her action, Dr. Bartlett would still have a *prima facie* moral obligation to keep her information confidential. One could argue that, since the obligation is only *prima facie*, it should be overridden by the *prima facie* obligation to try to prevent harm—especially if Mrs. Durham cannot articulate any good reasons for keeping the information confidential. However, in this case, I think that another option is available to Dr. Bartlett that would allow him to keep Mrs. Durham's information confidential and prevent harm to Mrs. Weir. He could meet with Mrs. Weir and simply recommend that she get tested for the BRCA1 mutation. I could imagine the conversation going as follows:

Dr. Bartlett: Mrs. Weir, I wanted to bring you in today to discuss something with you. I have recently come to believe that you may be at increased risk of breast and ovarian cancer due to possibly possessing a genetic mutation. I would like to get you tested,

because if you have this mutation there may be some things we can do to decrease your risk. The test involves obtaining a blood sample.

Mrs. Weir: Dr. Bartlett, why do you think I might have this mutation?

Dr. Bartlett: I am not at liberty to give you all the details of how I have come to believe that you might have this mutation, but I do think it is in your best interest if we had you tested. As your doctor I am asking you to trust me.

Trust is a ubiquitous part of the patient-physician relationship. And, while respect for patient autonomy is an extremely important ethical consideration that plays a fundamental role in the patient-physician relationship, respect for patient autonomy does not eliminate the need for patients to trust physicians, and it does not eliminate the need for physicians to be worthy of that trust. Sometimes trust is needed because the patient may not be able to understand or have enough time to process the information to make a decision without relying heavily on the physician's recommendation. In this case, trust is needed because the physician is trying to avoid violating a *prima facie* obligation to one patient while also trying to meet his *prima facie* obligation to prevent harm to another patient.

At this point, one might object. What if Mrs. Weir surmises that her sister has the mutation and that this is why Dr. Bartlett wants to have her tested? Suppose Mrs. Weir asks Mrs. Durham if she has the mutation? I think that both are possible outcomes, but even if Mrs. Weir does come to the conclusion that her sister has the mutation, Dr. Bartlett has not violated Mrs. Durham's confidentiality. He has not told Mrs. Weir anything about her sister's condition. He has only used that information to help another one of his patients. And while I think a case can be made that Dr. Bartlett should not directly divulge or negligently expose Mrs. Durham's personal health information to a third party, it is much harder to make the case that Dr. Bartlett should not use the information he has obtained to prevent a possible harm to a third party merely because doing so may increase the chances of that third party correctly surmising something about Mrs. Durham's health condition.

Suppose, for example, a college student contracts meningitis in a dorm and doesn't want anyone to know that she has it. Would the college student's desire to keep her health information private also preclude someone's sending letters to her dormmates about their need to get prophylaxis, because they might be able to deduce who was originally infected? I don't think so. The point here is that when one patient's confidential medical information can be used to prevent a serious harm to a third party, the *prima facie* right to confidentiality must be balanced against the *prima facie* obligation that the physician has to prevent serious harm to that third party. And while patients have a strong *prima facie* right to expect that physicians will not directly disclose or negligently expose their

health information, the claim to a right that physicians do everything possible to prevent others from surmising on their own some detail about a patient's health information is a far weaker claim. Suppose, for example, one patient sees another come to see an oncologist while in the waiting room and surmises that this person is being evaluated or treated for cancer. Are physicians obliged to prevent such occurrences? This seems to demand too much.

When divulging confidential information to prevent harm to a third party, I believe physicians should be guided by two principles. First, the harm should be both likely and significant [6]. The *prima facie* right to a physician's confidentiality is strong—the patient-physician relationship depends on it—and it takes a strong counterclaim to override it. Second, the physician should divulge only the information necessary for the third party to avoid the possible harm. Divulging other information would break confidentiality for no good reason. In our case, the potential harm is great and the amount of information that needs to be divulged can be minimized to the point that there is no direct disclosure of any of Mrs. Durham's confidential information.

In conclusion, Dr. Bartlett should talk to Mrs. Durham about why he believes it is important that her sister be tested and ask her to either tell her sister or allow him to discuss the positive BRCA1 test results with her sister. If Mrs. Durham refuses, Dr. Bartlett should reassure Mrs. Durham that he will not reveal to her sister that she has been diagnosed with ovarian cancer or with the BRCA1 mutation. He should then meet with Mrs. Weir, counsel her to get tested, and if she inquires why, inform her that he is not at liberty to say but would like for her to trust that he is trying to act in her best interest. This course of action would avoid violating Dr. Bartlett's *prima facie* obligation to keep Mrs. Durham's diagnosis confidential and fulfill his *prima facie* obligation to help prevent harm to Mrs. Weir.

References

1. For one famous version of act consequentialism, see Mill JS. *Utilitarianism*. Sher G, ed. Indianapolis, IN: Hackett Publishing Company; 1979.
2. Brody B. *Life and Death Decision Making*. New York, NY: Oxford University Press; 1988.
3. Beauchamp TL, Childress JF. *Principles of Biomedical Ethics*. 6th ed. New York, NY: Oxford University Press; 2008.
4. For a useful summary of moral dilemmas, see McConnell T. Moral dilemmas. In: Zalta EN, ed. *Stanford Encyclopedia of Philosophy*. Revised June 30, 2014. http://plato.stanford.edu/archives/fall2014/entries/moral-dilemmas/. Accessed June 14, 2015.
5. For an example of this type of approach, see Ross WD. *The Right and the Good*. Indianapolis, IN: Hackett Publishing Company; 1988.

6. For a classic court case that has influenced thinking about breaking confidentiality to prevent harm to third parties, see *Tarasoff v. Regents of the University of California*. In: Beauchamp TL, Walters L, Kahn JP, Mastroianni AC, eds. *Contemporary Issues in Bioethics*. 7th ed. Belmont, CA: Thomson-Wadsworth; 2007:140-148.

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The people and events in this case are fictional. Resemblance to real events or to names of people, living or dead, is entirely coincidental.

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ETHICS CASE

Oncofertility for Adolescents: When Parents and Physicians Disagree about Egg Cryopreservation for a Mature Minor

Commentary by Annekathryn Goodman, MD

Evelyn is 15 and was recently diagnosed with a rare small cell cancer of the left ovary. Although she was able to undergo fertility-sparing surgery with preservation of her uterus and right ovary, metastatic disease was found in the para-aortic nodes at the level of the renal vessels. Her treatment will include pelvic irradiation and six cycles of cisplatin, paclitaxel, and etoposide, all known gonadal cytotoxic chemotherapeutic drugs. Her gynecologic oncologist, Dr. Clark, is familiar with the data on adolescent fertility preservation through egg and sperm banking, a concept known as oncofertility.

Because Evelyn is a minor, Dr. Clark approaches the topic of oncofertility with her parents. Evelyn's mother and father both opposes bringing the topic up with their daughter because they feel she is too young to consider how fertility and infertility would affect the rest of her life and does not have the maturity to make that decision.

Dr. Clark wants to provide the best possible care for Evelyn, and this includes informing her of all the risks and benefits of her treatment. Moreover, he believes that it is his responsibility to present to Evelyn all the possible means of achieving a high quality of life following her treatment. He can't help but think that one day Evelyn will appreciate the fact that she still has the options to have children from her own eggs, even if she ultimately chooses not to do so. He explains his reasoning to Evelyn's parents, but they persist in their decision that Evelyn not be offered the intervention. They ask about the egg retrieval process for oncofertility, and Dr. Clark's answer reinforces their decision. Adding an oocyte retrieval procedure to radiation and chemotherapy is just too much to put Evelyn through, they say.

Commentary

Delivery of medical information and appropriate counseling about medical choices is an essential duty of health care professionals. This case raises important issues about informed consent and the rights of minors to make their own decisions. There is a delicate balance to delivering information to an adolescent patient with a life-threatening condition, counseling concerned and protective parents about medical choices, and advocating for a minor patient when parental decisions are at variance with a physician's recommendation. In this article, I examine the mandate of informed consent and legal views of adolescent decision making, review the long-term fertility

consequences of aggressive oncologic care for the adolescent and young adult, and consider their impact on personal well-being. I examine the ethical dilemma of not disclosing information and the tension between respecting parents' wishes and informing a minor about consequences that will impact her as an adult. In light of these legal, medical, and ethical considerations, I suggest possible solutions for how Dr. Clark can approach both the patient and her family to ensure that a fully informed consent discussion takes place and that respect for the patient's autonomy is preserved.

Informed Consent and the Patient Bill of Rights

Adult patients have a right to receive information about all available treatment options (including no treatment) and the risks and advantages of each before consenting to treatment. A necessary component of informed consent is that patients must understand the consequences of the various options that they may experience long afterward. Informed consent is an essential tenet of patient rights and the standard prequel to any treatment intervention for an adult patient, whether the setting of the medical care is outpatient, inpatient, or an emergency department [1]. Consent is an informed and voluntary decision to proceed with a medical intervention. The decision of a competent person supersedes the advice and recommendations of the doctor. Because patients have the right to determine what happens to their bodies, a doctor cannot touch or treat a patient without that patient's consent.

In the Consumer Bill of Rights and Responsibilities put forth by President Clinton's Advisory Commission on Consumer Protection and Quality in the Health Care Industry [2], information disclosure (chapter 1) and participation in treatment decisions (chapter 4) are central points. Table 1 summarizes information the patient must receive to be considered informed enough to consent. In providing information about the risks and benefits of the recommended treatment intervention, its success rates, and alternative approaches, the clinician must use language that is understandable to the patient, including using interpreters when the patient is not fluent in English.

Table 1. Topics to be covered in an adequate informed consent process

Elements
Description of procedure or treatment
Explanation of risks and benefits
Description of alternative treatment(s)
Description of anticipated outcome if no therapy is given
Description of anticipated short-term consequences of treatment, including length and challenges of recuperation
Description of anticipated long-term consequences of treatment, including permanent alterations to the body

A legal guardian has the duty to decide on medical care when a patient is either incompetent or younger than the legal age of consent, 18 years. This duty derives from the general presumption that parents or guardians will act in the best interest of their children and, legally, from the constitutional right to privacy regarding family matters and the common law rule of parental consent [3].

In the past, minors were not considered legally capable or competent to make medical decisions because of their age [4]. In the past 50 years, the courts have gradually recognized that minors who show maturity and competence deserve a voice in determining the course of their medical treatment [3]. Empirical evidence has revealed that children may be more capable of participating in their medical decisions than previously thought [5]. Legally, the definition of consent requires that an individual give permission voluntarily and with the understanding that he or she is consenting to some form of medical intervention [6]. In addition, the consenting individual needs to cognitively understand and have the ability to explain back the details of the medical intervention. Cognitive development at the ages of 11 to 13 and older correlates with the capacity for legal consent, according to developmental psychological research [5]. In certain situations, depending on the state [7], minors are deemed "mature" and therefore able to consent to treatment without the involvement of a parent or guardian. The "mature minor doctrine" is the common law rule that allows an adolescent who is mature to give consent for medical care [8]. The assessment of competence is based more on the child's functional ability than age [9].

"There are also statutory exceptions to the rule of parental consent regarding emergency care, sexually transmitted diseases, drug treatment, mental health care, pregnancy, contraception, and emancipation" for adolescents older than 14 years of age [10]. Table 2 summarizes situations in which a minor has the legal right to make medical decisions [3]. Specific details of the situations in which minors may consent independently to medical decisions vary by state in the United States [7].

Table 2. Conditions allowing minors to consent to medical treatment

Marriage
Past pregnancies
Seeking treatment for: • Drug abuse • Alcoholism • Mental and emotional disorders • Sexually transmitted disease • Rape
Being medically screened at a detention center

In the United States, "judges have decided that the ability to consent to a treatment implies the ability to refuse it.... This has led to the development of the concept of 'assent'" [11]. When children have the cognitive competence "to have some appreciation of a procedure, but not enough competence to give fully informed consent," they are considered able to "assent" or "dissent," often around the age of twelve [11]. There are three different categories of consent by minors: consent without their parents' consent or knowledge; the power to dissent when their parents have consented to their treatment; and the "right to know" even when the minor is not considered competent to make decisions [5, 12].

Reproductive Consequences of Cancer Therapy

Both chemotherapy and radiation can be ovariotoxic and lead to premature ovarian failure [13]. The Childhood Cancer Survivorship Study (CCSS), a large retrospective cohort study following the outcomes and long-term effects of childhood cancer in 5,149 women, found that childhood cancer survivors were less likely than their siblings to ever become pregnant, with a relative risk of 0.81 (95 percent CI, 0.73to 0.90; $p < .001$) [14].

A range of interventions, from ovarian suppression to surgical transposition of ovaries outside of the radiation field, has been tried to preserve ovarian function [15]. As this case scenario makes clear, one alternative is to preserve ovarian tissue and oocytes for future reproduction in the event that the ovaries lose function. In a center with multidisciplinary resources, fertility preservation procedures will not cause a significant (and perhaps risky) time lag before starting cancer therapy: in a single-institution study in which 96 female patients were referred for oocyte retrieval for cryopreservation [16], the mean time between counseling and retrieval was 15 days. There was no delay in oncologic treatment, with a mean time from laparoscopy to initiation of therapy of 4 days.

Qualitative research on adult survivors of adolescent cancers has identified the profound importance of addressing fertility concerns, which can affect relationships, personal well-being, and life planning [17]. In interviews of 45 adults, cancer therapy during adolescence and its impact on fertility was identified as disrupting personal identities, plans, and values [18]. Findings from in-depth interviews with 38 survivors of adolescent cancers suggest that adolescents can cope with information about fertility options alongside a discussion of cancer [19]. In the same study, women who did not receive fertility services as adolescents reported great distress and regret as adults [19]. Overall, this research has identified the importance of loss of fertility to the disruption of cancer survivors' personal narratives.

Ethical Considerations

The Declaration of Human Rights identifies the right to a family as a basic human right [20]. Given our ability to preserve cancer patients' fertility, clinicians have a duty to advocate for fertility-preserving measures as part of cancer care.

There is also now significant legal precedent for treating minors with respect, acknowledging their autonomy as persons, and including them in discussions about medical therapies [3, 5, 9-11]. Given the importance of fertility to a person's life plan, the parents' wishes in this case are at variance with the best medical care for Evelyn and her future quality of life. If Evelyn's oocytes can be retrieved and frozen, she will retain the choice to have biological children. If she is not given this option, she may perceive herself as being harmed because her life plans have purposefully been disrupted. A lack of action during the patient's adolescence, specifically not offering fertility preservation options, is a violation of the ethical principle of nonmaleficence.

Finding Solutions

The ideal solution to Dr. Clark's dilemma is to convince the parents that presenting fertility options to Evelyn is the right thing to do. Based on the principle of the "right to know," professional guidelines, and the common law rule, Dr. Clark could consider approaching Evelyn to discuss her treatment options even without seeking parental consent to talk with her [9, 12, 15]. However, without the parents' buy-in to this discussion, there is the risk that they may look for care elsewhere and consequently that Evelyn will not have the opportunity to consider fertility-sparing options. The first step is to explore the parents' concerns fully. Are they just overwhelmed by what Evelyn is facing? Are there any cultural or religious concerns about assisted reproductive techniques? The second step is to get to know Evelyn. What is her understanding about her cancer? What are her hopes and dreams about her future? From these conversations, Dr. Clark will be able to assess Evelyn's cognitive and decision-making abilities. He might also refer the family for a consultation with a clinician at another institution because second opinions can help clarify issues, confirm treatment recommendations, and potentially explore different treatment options [21].

When there is potential conflict with the legal guardians of a patient, it is important to bring in help and not negotiate alone. Various consultative services are available at cancer centers such as the ethics committee, social services, chaplaincy, and adolescent medicine specialists. A family meeting with several specialists may help to address the parents' concerns and provide expert guidance. In addition, other adolescent patients and their parents who have been through both cancer therapy and fertility preservation may give vital peer-to-peer support and advice. Resources Dr. Clark can draw upon are listed in table 3.

Table 3. Resources for conflict resolution with parents

Medical • Adolescent medicine • Reproductive endocrinology • Psychiatry • Palliative care
Supportive services • Social services • Chaplaincy
Hospital services • Legal council • Ethics committee
Peer group support • Parental peers • Adolescent peers

Conclusion

One of the pillars of health care is to respect the autonomy of the patient by obtaining informed consent to treatment. Minors deserve special protection but are also entitled to basic rights. They are increasingly autonomous, both developmentally and in legal terms, from 11 to 18 years of age [5]. When a clinician and the parents of a minor patient disagree about providing the patient with all the options for future fertility, a multidisciplinary intervention should be considered. The best possible outcome of both cancer treatment and fertility preservation can be realized for an adolescent patient with counseling, education, and peer support.

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MEDICAL EDUCATION

Designing an Ethics Curriculum in Obstetrics and Gynecology

Matthew Schlumbrecht, MD, MPH

The obstetrics and gynecology specialty addresses issues that span from preconception to end of life; hence, the obstetrician/gynecologist encounters the need to call upon ethical principles to assist in decision making and providing optimal care for women on almost a daily basis. While greater skill in the application of ethical principles evolves with ongoing engagement with patients, a knowledge base and methods for approaching challenging situations in a supportive environment are crucial for medical students, residents, and fellows. For residents and fellows, time on the gynecologic oncology service provides an opportunity for the application of ethical principles to real patients and cases. Developing a curriculum that allows medical trainees to engage ethically challenging situations with confidence and thoughtfulness is imperative to shaping well-rounded physicians.

The Council on Resident Education in Obstetrics and Gynecology (CREOG) requires that residents graduating from accredited programs demonstrate a commitment to adherence to ethical principles as part of their professional development [1]. Specifically, CREOG mandates that graduates be able to describe basic ethical concepts such as respect for autonomy, beneficence, justice, and nonmaleficence; be familiar with the meaning of informed consent; demonstrate an understanding of the use of living wills and durable power of attorney; and comfortably engage in discussions about withdrawal of care, including "do not resuscitate" orders [1]. Similarly, the American Board of Obstetrics and Gynecology (ABOG) requires that gynecologic oncology fellows understand and practice ethical medicine, including appropriate professional conduct, addressing patient and family care needs, and using advanced directives [2]. Acknowledged by the Accreditation Council on Graduate Medical Education (AGCME) as a component of the core competency "professionalism," adherence to ethical principles is a requirement for successful completion of a program [3].

Despite the universal agreement that ethics education is an important component of any medical training curriculum, it is questionable whether the drive to implement such programs has been successful in obstetrics and gynecology. A recent survey of 118 ob-gyn residency program directors found that only 50 percent of programs had incorporated ethics into their core curricula and that most ethics training did not follow a standard curriculum to be used repeatedly [4]. Fewer than five hours of ethics training per year was provided in more than half the programs [4]. More than 70 percent of

respondents indicated that they would like to incorporate more ethics education and that they thought it should be a required component of residency training, but less than 40 percent were familiar with relevant resources, such as the Association of Professors of Obstetrics and Gynecology (APGO)/CREOG ethics case study [5]. Barriers to increasing the amount of time for ethics training included an already overcrowded curriculum and lack of faculty expertise in ethics topics [4].

Unfortunately, these data are not that dissimilar from a survey of ethics education in ob-gyn residency programs performed more than 20 years ago. In the report by Cain et al. [6], the average amount of time for ethics training for residents was only four hours; faculty members lacked training in medical ethics; and the method of teaching was generally lacking in structure.

Designing a Curriculum: Things to Take into Account

In designing a medical ethics training program, the first concern is what should be included in a curriculum. With increasing duty-hour restrictions, time is at a premium. As with all didactics, time needs to be protected so that clinical duties do not supersede nonclinical educational opportunities, but the topics to be covered should also be beneficial, relevant, and engaging: for example, while consideration of pregnancy termination for genetic malformation may be important on an antepartum ward, it has no place on the gynecologic oncology service.

Identify the most important topics. Although identifying which ethical topics are most important would seem to be an easy problem to solve, the perception of which issues are most important appears to vary by level of training. In 2006, Goold and Stern [7] reported on a survey that asked medical residents and a group composed of ethics committee members, patient advocates, practicing physicians, and program directors to select ethical themes upon which to develop a focused curriculum. Although trainees selected "family interactions" as the most important theme for education, the nontrainee group—with more experience to draw upon—selected "informed consent" as the most important theme. The authors argued that opinion or anecdotal experience alone may not provide a strong enough foundation for curriculum development.

At the University of Texas MD Anderson Cancer Center, we addressed this conflict by designing a gynecologic oncology ethics education program around the results of a retrospective review of all ethics consults completed at a tertiary cancer center over a period of 15 years [8]. The most common clinical case types, including level of appropriate treatment (i.e., code status), withdrawal of care from an incompetent patient, surrogacy, futility of treatment, and obligations to a noncompliant patient, were identified and used as the basis for a quarterly ethics education program for gynecologic oncology fellows.

Don't assume everyone will share the same ethical approach. A second consideration in curriculum design is diversity amongst the trainees. Medical school graduates not only come from different regions, but also vary by gender, ethnicity, sexual orientation, religious background, and other traits. Recognizing this diversity is crucial because these personal attributes contribute much to the individual's baseline approach to complicated ethical questions. A survey of Canadian obstetrics and gynecology residents asked about factors that most influenced their individual decision-making processes to gain an understanding of potential biases [9]. Residents indicated family views as being the most influential factor in their decisions (34.2 percent), followed by previous learning during undergraduate work (17.1 percent), religious background (15.4 percent), residency training (11.1 percent), and peer attitudes (9.4 percent) [9]. These findings underscore the importance of developing a curriculum that allows open exchange of ideas in a nonthreatening setting. The introduction of medical ethics principles provides a common lens through which students can examine and perhaps alter their biases.

Structure programs to engage trainees. A key component of any curriculum is engagement of the trainee. If the resident or fellow is disinterested or detached, assimilation of knowledge is unlikely. Multiple ethics education models have been suggested to connect trainees to the topics being explored. Mueller and Koenig [10], for example, have recommended that ethics consults themselves be the basis for a training initiative, inasmuch as they reflect the actual experiences of patients and physicians and highlight important ethical topics seen in clinical practice. Although this model would provide trainees with direct patient contact that may be meaningful, clinic responsibilities might limit its success.

Researchers have also demonstrated that use of small groups is a feasible and successful way to augment learning and application of ethics principles. For example, Smith et al. [11] performed a direct comparison of the effects of two teaching methods on medical students' recognition and assessment of common ethical dilemmas in three case scenarios. One cohort submitted responses to a professor who then provided feedback. A second cohort participated in a discussion group about the cases and then submitted evaluations of them. It was found that the students in the discussion group had improved recognition and assessment of ethical issues and greater ability to formulate a plan. Similar problem-based learning models have been advocated for use as early as the first year of medical school as a way to introduce professional behavior, challenging students to explore their own values, become active learners, and thoughtfully engage complicated situations with peers [12, 13].

In addition, trainees should be invited to participate in decisions about how best to achieve their educational goals, and educational sessions should be provided in an interactive format.

Tailor efforts to each program and institution. In designing an ethics curriculum for trainees in obstetrics and gynecology and gynecologic oncology, the considerations above are all important. For the curriculum to be successful, it needs to be engaging, relevant, effective, and efficient. It would be a disservice to think that what works for one program will be universally successful for all. Residency and fellowship training programs are as diverse as the young physicians they attract, with differing resources and patient populations. The unique features of each training hospital should be explored as ways to highlight and promote discussion about specific ethical principles. For example, in a hospital that provides care for an underserved patient population, there will be opportunities to discuss the principle of justice and equitable allocation of health care resources (e.g., access to pap smear screening for cervical cancer).

Furthermore, the particular institution's resources should be tapped. At the very least, a member of the institutional ethics board, and preferably a clinical ethicist, should be invited to participate in curriculum development. People in such roles are highly trained and provide a different, and frequently enlightening, perspective from that of supervising clinicians.

Conclusion

As residency and fellowship training requirements continue to evolve, so, too, will ethics curricula. It is incumbent on trainees and programs alike to recognize the importance of ethics education and advocate for appropriate opportunities to hone the skills required to critically assess ethical dilemmas that graduates will undoubtedly face. Competency in ethics truly is a measure of professionalism, and as a community of obstetricians-gynecologists and gynecologic oncologists, we are obligated to train young physicians to be capable of delivering comprehensive and meaningful care to women.

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IN THE LITERATURE

After Equipoise: Continuing Research to Gain FDA Approval

Allison Kerianne Crockett, MD

Krill LS, Adelson JW, Randall LM, Bristow RE. Clinical commentary: medical ethics and the ramifications of equipoise in clinical research. Is a confirmatory trial using a non-bevacizumab containing arm feasible in patients with recurrent cervical cancer? *Gynecol Oncol*. 2014;134(3):447-449.

"First, do no harm." On the surface, this is the most well-known, easy to understand, and easy to follow mandate given to us as we evolve into doctors. Of course a doctor should do no harm. Quite the opposite—a doctor is meant to care for, heal, and generally do *good*. Most of us chose this career specifically so that we might have that opportunity each day. In medical ethics classes, we learned the basic principles of ethical health care: respect for autonomy, nonmaleficence, beneficence, and justice. As we mature from early medical students to clinical medical students, residents, attending physicians, and perhaps researchers, so does our understanding of these principles and what it means to put them into practice.

In the world of clinical research, the principle of equipoise is basically an application of the principle of nonmaleficence to the process of comparing medications and treatments. It means that, for a study to be ethical, an individual researcher must truly not know whether one treatment has advantages over another when enrolling patients and conducting research [1]. This idea was first proposed by Charles Fried in his 1974 book *Medical Experimentation: Personal Integrity and Social Policy* [2]. It was expanded upon by Benjamin Freedman in his 1987 essay, "Equipoise and the Ethics of Medical Research," in which he proposed that, for a study to be ethical, it's more important for the expert medical community, rather than for an individual researcher, to be in a state of uncertainty regarding the superiority of one treatment or another [3].

In the article to which I am responding [4], Krill and colleagues discuss the Gynecological Oncology Group (GOG) 240, a phase-3 clinical trial in which the antiangiogenesis agent bevacizumab was added to cytotoxic chemotherapy regimens to treat recurrent, metastatic, and persistent cervical cancer. During the second interim analysis, the bevacizumab arms of the study demonstrated significantly improved overall survival of three months compared to chemotherapy alone, regardless of the cytotoxic chemo agents with which they were paired [5].

The National Comprehensive Cancer Network (NCCN) updated its clinical practice guidelines to include bevacizumab for the treatment of advanced cervical cancer, which qualified it for coverage by most private US insurance companies [4]. The National Health Service of England also approved bevacizumab as a first-line treatment. But the US Food and Drug Administration (FDA), which requires more extensive study before approving an agent, was not so quick to accept this modification to approved regimens [4]. Since the Krill et al. article was published in June 2014, the FDA evaluated the use of bevacizumab under its priority approval program and ultimately added recurrent, persistent, or metastatic cervical cancer as indications for use in August 2014 [6]. But let's suppose for a moment that it hadn't.

This lack of approval would have meant that Medicare and Medicaid patients with recurrent, metastatic, or persistent cervical cancer could not have obtained coverage for bevacizumab [4]. For those in the United States without private insurance, this agent is surely cost-prohibitive; a single dose costs several thousand dollars [7]. To close this gap in coverage would require gaining FDA approval through more study. Without FDA approval and subsequent coverage by Medicare and Medicaid, the disparity in outcomes between the privately insured and everyone else would remain. Conversely, continuing the investigation of the safety and efficacy of bevacizumab to facilitate FDA approval and effectively improve access for a broader range of patients would require researchers to subject some participants to chemotherapy alone, expecting that their survival time would be shorter than that of the participants in the experimental arm. Such an arrangement would directly violate the fundamental principle of equipoise [2-4].

In imagining that bevacizumab had not gained FDA approval, my first reaction to the Krill et al. article was in favor of continued investigation of bevacizumab for cervical cancer, so that it might become FDA-approved and therefore available to more patients. I doubt the concept of equipoise was ever meant to limit research in such a way that populations of people would be excluded from the progress generated by clinical trials. It's reasonable to assume that the principle of equipoise was introduced to hold researchers and physician-researchers accountable and prevent them from conducting sham trials with predictable outcomes just to get a "positive" result published. This principle also acknowledges the tremendous value of the countless anonymous patients whose participation, and sometimes deaths, provide answers, warnings, and hope for countless more patients who will benefit from the lessons learned and therapies developed.

On the other hand, what is the value, for lack of a better word, of three additional months' survival? What was the content and quality of those extra three months for patients and their families? Did the majority of patients experience three pain-free, carefree months of checking things off their proverbial bucket lists and soaking in precious moments with their favorite people? Or were they three months filled with doctors' office waiting rooms, mounting medical bills, artificial nutrition, infections,

leaking ostomies, and untreatable pain? If they could tell us, would those who experienced the latter want to live those three months again? Are Medicare, Medicaid, and uninsured patients really missing out on much?

Of course these questions can only be answered by an individual patient in the context of his or her own beliefs, priorities, and values. It's almost certainly my perspective as a young, able-bodied person at this point in time that suggests to me that only three months enjoyed with friends, family, and adventure are worth living. But perhaps the point is that each patient is entitled to the option of the treatment that might give him or her those three months, whatever they may bring, regardless of socioeconomic and insurance status. Ultimately, I can't condone the idea of denying people access to these treatments.

Had FDA approval not been gained, which of the two options would have posed less harm: To have discontinued the study of bevacizumab in the treatment of advanced cervical cancer, which would have precluded FDA approval and subsequently left an entire group of people—those without private health insurance—without access to a treatment for an indefinite period of time? Or to have continued to study how chemotherapy *with* bevacizumab compared to chemotherapy *without* it, thereby directly violating the standard of equipoise. Neither of these options is acceptable.

Thankfully, in the case of bevacizumab, we didn't have to settle for either. However, there will be another case like this, where the various sectors that make up the medical community struggle to agree on a best course of action and where the path that "does no harm" is not quite as clearly defined as it once seemed. Just as physicians and researchers must make it a priority to do no harm, so must the governing and regulating bodies who establish the policies and protocols to which we must adhere.

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STATE OF THE ART AND SCIENCE

Fallopian Tube Ligation or Salpingectomy as Means for Reducing Risk of Ovarian Cancer

J. Brian Szender, MD, MS, and Shashikant B. Lele, MD

The Problem of Ovarian Cancer

Ovarian cancer remains the most lethal gynecologic malignancy in the United States, both in rate of fatality (64 percent of patients ultimately die of their disease [1]) and in overall deaths (14,270 in 2014 [2]). Although 50-75 percent of patients treated with chemotherapy initially respond to the medications, most will have recurrences of the disease [1]. The driving force behind the poor survival rates is the stage at diagnosis. Approximately 65 percent of patients present with widespread (stages III or IV) disease, at which point cure is uncommon [2]. For patients with stage I disease, on the other hand, five-year survival rates exceed 90 percent [2].

One reason that most patients are diagnosed at late stages is that the clinical symptoms of ovarian cancer usually do not become apparent until the disease has disseminated throughout the peritoneal cavity. Although multiple attempts have been made to develop screening programs aimed at detecting early-stage disease, current screening methods are fraught with low sensitivity and specificity, high false-positive rates, and an unfavorable balance between the risks of early intervention and the benefits of cancer risk reduction [2-4].

Attempts at Ovarian Cancer Screening

Because the clinical symptoms of ovarian cancer are vague and often appear late in the course of disease, numerous attempts have been made to initiate screening programs to identify preclinical disease in asymptomatic women [3]. Some methods for screening include pelvic examination, ultrasound, and blood testing. The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial found that screening did more harm than good with respect to ovarian cancer [3]. Specifically, study subjects underwent unnecessary surgeries that did not diagnose ovarian cancer and were associated with intraoperative and postoperative complications. The United Kingdom Collaborative Trial of Ovarian Cancer Screening, published in 2015, found that serial testing of the cancer antigen (CA) 125 protein, interpreted according to the Risk of Ovarian Cancer Algorithm (ROCA), and ultrasound were better at detecting ovarian cancer than a single threshold CA 125 test [5]. Ultimately, screening for ovarian cancer is not ready for application outside of clinical trials because the results have not been

validated in independent cohorts. Clinicians must maintain a high index of suspicion, i.e., consider ovarian cancer a likely possibility, to clinically diagnose it.

Due to the absence of an effective screening algorithm for assessing risk or clinical symptoms that develop with early-stage disease, primary prevention strategies are crucial for reducing ovarian cancer-related deaths.

Experience from Hereditary Breast and Ovarian Cancer Syndromes

Identifying patients at increased risk for ovarian cancer is key to prevention, early detection, and, ultimately, improving survival. Those with BRCA1 mutations have a 39-46 percent lifetime risk of ovarian cancer, those with BRCA2 mutations have a 10-27 percent risk, and up to 24 percent of those with Lynch syndrome will develop ovarian cancer [6]. At this time, the best tools that clinicians have for ovarian cancer prevention are a thorough family history and testing appropriate patients for genetic susceptibility [7]. The Society of Gynecologic Oncologists (SGO) policy statement on genetic counseling says unaffected individuals with increased risk—i.e., relatives with ovarian cancer; a family history suggestive of Lynch syndrome based on Amsterdam Criteria or Bethesda Guidelines; known mutations in the family or a family member diagnosed with breast cancer before age 45; multiple breast cancers, male breast cancer, pancreatic cancer, or aggressive prostate cancer (with a Gleason score of 7 or above)—should be referred for genetic counseling and, potentially, testing for germline mutations in BRCA [7]. If BRCA mutations or Lynch syndrome are identified, the National Comprehensive Cancer Network (NCCN) recommends removal of both fallopian tubes and ovaries between the ages of 35 and 40, based on the particular mutation carried. CA 125 tests and pelvic ultrasound have been considered, but there is not sufficient evidence that these tests are sensitive or specific enough to obviate the need for surgery [8].

Fallopian Origin and Prevention of Ovarian Cancer

A proposed model for ovarian carcinogenesis arising in the fallopian tube has emerged over the last decade [9, 10]. This tubal-origin hypothesis has gained traction with identification of pre-invasive lesions in the fallopian tubes of high-risk patients undergoing risk-reducing surgery [10]. Thus, bilateral salpingectomy with ovarian conservation was proposed as a "middle-ground" method of primary prevention, with the benefit of removing potential tissue of origin and without the risks of surgical menopause. This method has been proposed for clinical trials in high-risk patients, but results are not currently available [11]. The SGO in 2013 published a clinical practice statement recommending that a bilateral salpingectomy should be considered "at the time of abdominal or pelvic surgery, hysterectomy, or in lieu of tubal ligation" [12]. The American College of Obstetricians and Gynecologists (ACOG) had a more tempered statement, saying that salpingectomy should be considered for population-risk patients, i.e., those without increased risk based on personal or family history, but they were clear that the approach to pelvic surgery, hysterectomy, or sterilization should not change

simply to increase the chances of completing bilateral salpingectomy [13]. Both of these statements were more conservative than the proposed plan of the British Columbia Ovarian Cancer Research Group program, instituted in 2010, which involved performing opportunistic salpingectomy with benign hysterectomy or in lieu of bilateral tubal ligation for permanent contraception. These authors suggested that this approach would yield a 20-40 percent population risk reduction for ovarian cancer over the next 20 years [14].

The estimated risk reduction for any individual person undergoing opportunistic salpingectomy is up to 50 percent [14]. Although this is an appreciable benefit, it must be tempered with a reminder that women at population risk of ovarian cancer have only a 1:70 or 1.4 percent lifetime risk [14]. The significant benefits of opportunistic salpingectomy, besides the risk reduction, are the ease and speed of the procedure, the rarity of complications, the convenience of removing the specimen, and the fact that surgical removal is theoretically the only way to permanently reduce the risk of ovarian cancer [15] (although bilateral tubal ligation without salpingectomy has also been associated with decreased risk [16]). Whether salpingectomy is more beneficial than tubal ligation has not been established.

Unresolved Questions

Despite the popularity of salpingo-oophorectomy as a method of reducing risk of ovarian cancer, data from the Nurses' Health Study suggest that oophorectomy before age 47.5 years may be associated with increased risk of death from other causes, such as cardiovascular disease [4], and that the actual permanent risk reduction with salpingectomy, as opposed to the theoretical 50 percent reduction [14], is not entirely clear.

Numerous questions remain regarding the optimal timing of salpingectomy, as the timespan during which the ovaries are susceptible to induction of cancer from the fallopian tubes is certainly not infinitely large. A bilateral salpingectomy at age 30 is logically more effective at risk reduction than the same surgery at age 60. Unfortunately, the relationship between time and risk reduction has not been not characterized, and prospective studies of the effect of age at salpingectomy on risk reduction would require prohibitively large cohort sizes and long follow-up periods. Similarly, there are other commonly accepted interventions associated with risk reduction, including oral contraceptive pill use and breastfeeding [2, 15, 16]. It is not known how salpingectomy and oral contraceptive pill use interact with one another, although presumably women with a history of bilateral salpingectomy will use birth control pills less frequently, given that the prevention of unintended pregnancy is no longer a concern.

Another unresolved question is whether salpingectomy should be used instead of tubal ligation for a "two birds with one stone" approach to sterilization and risk reduction. Caution should be exercised when choosing salpingectomy over tubal ligation for

sterilization, not because of the inability to reverse salpingectomy—tubal ligation also should not be performed on women who may desire future childbearing, and in vitro fertilization is a viable method of achieving pregnancy after salpingectomy or tubal ligation [17]—but because "low-risk" surgery does not equal "no risk." We should be cautioned by prior experience with opportunistic appendectomy at the time of cesarean section or hysterectomy [18]: with opportunistic appendectomy, stump leaks, bleeding, and infection were all possible. Furthermore, salpingectomy increases the length of the operation, and length of surgery has consistently been identified as an independent risk factor for postoperative morbidity [19-23], so even an opportunistic salpingectomy can increase some risks.

Another issue is that payers may be reluctant to authorize the charges for risk-reducing procedures, given the number needed to prevent a single case of ovarian cancer. The theoretical number needed reported by Kwon and colleagues in 2015 was 273 for salpingectomy at the time of hysterectomy and 366 for salpingectomy in lieu of other tubal occlusion methods for sterilization [14]. Although these numbers are on the same order of magnitude as the number needed to vaccinate with the human papilloma virus vaccine in the United States [14], the costs associated with vaccination are less than the costs of salpingectomy.

Conclusions

Ultimately, we think ACOG's recommendation of a discussion about risks and benefits of removing both fallopian tubes at the time of hysterectomy is reasonable. However, we cannot place enough importance on the statement, "the approach to hysterectomy or sterilization should not be influenced by the theoretical benefit of salpingectomy" [13]. In the absence of results from prospective studies, which will not be available for decades, fallopian tubes should be removed when a convenient opportunity arises, but extensive surgery should not be attempted just for that purpose.

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HEALTH LAW

Supreme Court to Myriad Genetics: Synthetic DNA is Patentable but Isolated Genes Are Not

Richard Weinmeyer, JD, MA, MPhil, and Tobin Klusty

Ever since James Watson and Francis Crick presented the double-helix structure of DNA to the world in 1953, genetic research—and its contribution to medical science—has become an invaluable tool for understanding and fighting disease. The research has also sparked a race to publish, patent, and profit from discoveries to gain an advantage in a scientific marketplace in which time and money are finite resources and companies are made and others diminished by a single innovation. In *Association for Molecular Pathology v. Myriad Genetics, Inc.* [1], the United States Supreme Court was thrust into this rapidly evolving sphere of science to determine when a research result is patentable under federal law, allowing those who lay claim to the rights of a unique research finding the ability to control its future use.

The early 1990s were marked by intense international research on the genetic foundations of breast cancer [2]. In 1990, a research group at the University of California at Berkeley announced that they had located a gene on chromosome 17 that provided the first evidence of the connection between certain genetic variations and breast cancer [3]. That genetic variation would become known as BRCA1. The following year, a group of researchers from the University of Utah's Center for Genetic Epidemiology, with financial backing from the pharmaceutical company Eli Lilly, created a small biotechnology company, Myriad Genetics [4]. Myriad "sequenced" BRCA1—that is, identified the nucleotide bases in DNA that together comprise the gene—in 1994 and obtained patents covering the sequenced gene, more than 40 mutations or variations of BRCA1, and numerous diagnostic tests and methods for identifying mutations of the gene [4]. Myriad was also successful in creating a synthetic form of BRCA1—called cDNA—that contained only the "working parts" of the gene, those involved in the creation of mRNA, which is essential to protein synthesis [5]. Over the next four years, Myriad raced a scientific group in the United Kingdom to sequence another gene implicated in breast cancer, BRCA2, eventually filing for patents on that sequence, its mutations, and diagnostic tests based on the gene [6].

The significance of the work undertaken by Myriad and other scientific groups cannot be overstated. For the average American woman, there is a 12 to 13 percent risk for developing breast cancer, but for women who possess genetic mutations such as those on BRCA1 and BRCA2, the risk rises dramatically, to 50 to 80 percent for breast cancer

and 20 to 50 percent for ovarian cancer [7]. Having secured the patents on the genes, their mutations, and the tests to identify these genetic characteristics, Myriad aggressively sought to make use of its competitive advantage through the sales of its tests for these genes and their mutations [8]. The company sent cease-and-desist letters to researchers whose work involved isolating the genes and filed patent infringement suits against parties engaging in BRCA testing [9]. Following years of tumultuous relationships with the scientific community, health care organizations, physicians, patient advocacy groups, and individual patients, a lawsuit was filed against Myriad in 2010, challenging its patents on BRCA1 and BRCA2 and other patents stemming from these two genes.

On May 12, 2009, several research groups and doctors filed claims in the Southern District of New York alleging, among other things, that Myriad's BRCA1, BRCA2, and cDNA patents were invalid under 35 USC section 101 [10]. The district court granted the petitioners' motion for summary judgment, finding all three patents invalid under section 101 because the DNA segments were not separate from nature (including cDNA, because it "contains the identical protein coding informational content as the DNA in the body, even though differences exist in its physical form") [10]. But the petitioners' victory was not complete: Myriad appealed the decision, and the federal circuit court reversed it [11]. Following the reversal, the petitioners appealed to the US Supreme Court, which vacated the decision and sent the case back to the federal circuit court to be decided in light of *Mayo Collaborative Services v. Prometheus Laboratories, Inc.* [12], which had established that items or processes are not patentable unless they are themselves inventive or do not exist or occur without artificial modification [13].

The federal circuit court issued a new opinion, with two out of three of the judges concluding, for different reasons, that isolated DNA segments are eligible for patenting [14]. Judge Alan Lourie's reason was that the isolation process involved severing covalent bonds at both ends of a DNA segment, which technically formed molecules that do not occur naturally [15]. Judge Kimberly Moore also held that the BRCA1 and BRCA2 patents should stand, but due to Myriad's reliance on the patent's approval for profit and business development [16]. Even though Judge Bryson disagreed on the patent eligibility of isolated DNA segments, all three judges concluded that cDNA was eligible for patenting because it was created, not merely isolated, in a laboratory [17].

The decision continued the life of Myriad's patents, but the petitioners had one final move: in the spring of 2013, they asked US Supreme Court to address the legal question of whether human genes are patentable. As was the case with the federal district court and court of appeals, the question rested on the court's reading of the Patent Act and past precedent in this area of law. And, based on the Supreme Court's analysis, the answer was a resounding and unanimous "no."

Justice Clarence Thomas, writing for the court, stated that, while Section 101 of the Patent Act applies to "[w]hoever invents or discovers any new and useful…composition of matter, or any new and useful improvements thereof" [18], the court has "long held that this provision contains an important implicit exception[:] Laws of nature, natural phenomena, and abstract ideas" are basic tools and building blocks and, hence, "lie beyond the domain of patent protection" [18]. Patents exist to promote creation and to protect ideas, while the elements of nature are "free to all men and reserved exclusively to none" [18].

Myriad and the opposing parties were in agreement on an important point: Myriad did not create or alter the genetic information found within BRCA1 and BRCA2. What the company did was uncover the exact location and genetic sequence of the two genes within their respective chromosomes. To decide whether such a discovery could count as patentable, the court looked to two prior cases on this matter.

Diamond v. Chakrabarty [19] concerned the addition of four plasmids to a bacterium, enabling the bacterium to break down various components of crude oil. The court held that the modified bacterium was patentable because the addition of the plasmids rendered it new, "with markedly different characteristics from any found in nature" [20]. The court cautioned, however, that "[g]roundbreaking, innovative, or even brilliant discovery does not by itself satisfy" the Supreme Court's section 101 "law of nature" exception [21]. In the case of *Funk Brothers Seed Co. v. Kalo Inoculant Co.* [22], the patent in question was for a mixture of naturally occurring bacteria strains that helped plants extract nitrogen from the air and fix it in the soil, improving nitrogen levels, a discovery made by farmers [23]. This mixture was not deemed patentable by the court because the patent holder had not altered the bacteria in any way and thus the bacteria, whether on their own or mixed together, "fell squarely within the law of nature exception" [21].

The Supreme Court clearly understood the significance of Myriad's work on the BRCA1 and BRCA2 genes. It had identified and sequenced significant genes that would aid researchers and clinicians in their understanding and treatment of breast and ovarian cancers, "but separating that gene from its surrounding genetic material is not an act of invention" [21] and "discovery, by itself, does not render the BRCA genes" [21] patent-eligible. Justice Thomas even looked to Myriad's own patent descriptions to highlight the problem of the company's claim. Myriad thoroughly explained the "iterative process" for locating and sequencing the genes, but the patents mentioned neither changes made to the chemical structure of the genes nor a unique molecule that would deem their work patentable [24].

The only product before the court that was deemed patent-worthy was cDNA, a synthetically created DNA that contains the "same protein-coding information found in a segment of natural DNA but that omits portions within the DNA segment that do not

code for proteins" [25]. The justices reasoned that, although cDNA contains the same nucleotide sequence that is found in naturally occurring DNA, "the lab technician unquestionably creates something new when cDNA is made" [26]. While the petitioners in the case argued that cDNA should not be eligible for patenting because of the similarities of its nucleotide sequence to DNA, the court identified it as distinct from a "product of nature" [26].

The US Supreme Court's decision in *Myriad Genetics* is a critically important ruling amidst a scientific landscape that is changing more than most can comprehend. It helped to delineate the boundaries between those products of inquiry that are unearthed in their natural form and those that are the result of human innovation and creation. This should give those working on the cutting edge of genetics and medicine a clearer idea of which ideas can merely be lauded for their public good and which can also be pursued for private gain.

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MEDICINE AND SOCIETY

The HPV Vaccine: Overcoming Barriers to Acceptance of a Medical Triumph

Jennifer Emberger, MD, MPH

The human papillomavirus (HPV) vaccine is unique among vaccines because it can prevent cancer. Yet vaccination rates remain low, and incidence of HPV infection remains high. A lack of education regarding the causal link between HPV infection and cancer and the purpose of the vaccine seems to be partially responsible, complicated by issues related to race, sex, sexual orientation, and public misperception.

Background

It is estimated that 14 million people acquire new HPV infections annually in the United States [1]. HPV is currently the most common sexually transmitted infection in our country [1-4], with the highest prevalence in sexually active adolescents and young adults [1-3]. There are more than 150 types of HPV, 40 of which infect the genitals [1, 5]. Most HPV infections, whether they carry a high or low risk for cervical cancer, are asymptomatic and resolve spontaneously within 1-2 years [1-3, 6-8]. HPV is considered to be a necessary cause of cervical cancer; infection with high-risk HPV types is found in 99 percent of all cervical cancers [6], and persistent infection with high-risk HPV types contributes to the development of cervical cancer [2, 3, 6, 8, 9], other anogenital cancers [2, 3, 9], and oropharyngeal cancers [1, 9]. However, infection with HPV is not sufficient to cause cervical cancer; many women are infected with HPV but do not go on to develop cancer [6]. It also usually takes decades for cervical cancer to develop after infection with HPV [6, 7]. The extant vaccines are recommended to be given starting at age 11-12, ideally before initiation of sexual activity [2, 3, 7-9, 10], because they do not seem to protect against disease from HPV types that patients are already infected with [6, 7, 10]. However, even if a patient is already sexually active, the vaccine should prevent the patient from being infected with other HPV types [7, 10].

Low Vaccination Rates

One of the main ethical and social questions surrounding HPV vaccination is low vaccination rates. The vaccination rates among adolescents and young adults, for whom the risk of infection is greatest, remain low [2, 4, 6, 11]—lower than was true for other vaccines in their first years of initiation [2, 6]. Some reasons that surveyed parents have cited for not vaccinating their children for HPV include needing more information, no recommendation of vaccination by a physician, and the perception that their daughters are not sexually active [11]. Other barriers to vaccination include low frequency of health maintenance visits, cost (if the vaccine is not covered or the patient is uninsured), and

lack of understanding of disease risk [4]. Another possible contributor to low vaccination rates is concern that giving children the HPV vaccine will encourage sexual promiscuity [12]. Similar arguments have been made against discussing safe sex and making condoms accessible to adolescents. But, as clinicians, what we can and should do is educate and equip our patients to protect *themselves* from acquiring sexually transmitted diseases that could affect them for the rest of their lives. A theoretical risk that a patient will be somewhat more likely to engage in sex because he or she is more protected from adverse health consequences should not supersede a clinician's duty to offer counseling, education, and interventions to prevent infection with preventable diseases. Parents and patients need to be educated on the burden of HPV infection and the benefits of vaccination.

It has been shown that physician recommendation is a major factor in vaccine initiation [9, 11]. Discussing HPV vaccination at every well-child check starting as early as age 9, but at the very least at ages 11 or 12, should help to increase acceptance of the vaccine and increase vaccination rates.

Recommendations and Utilization Rates by Subpopulation

A second issue surrounding the HPV vaccine is that, although it has been proven that HPV affects both men and women [5], recommendation and promotion of the vaccine for men has lagged behind approval and recommendations for women. While the most recent, nine-valent HPV vaccine was approved in December 2014 for use in both men and women [13], the two earlier vaccines were first approved only for women. When the first, quadrivalent HPV vaccine was licensed in 2006, it was only licensed for use in girls and women [7], and it was not until three years later that it was approved to prevent genital warts in boys and men [14]; a second HPV vaccine—the bivalent vaccine—was licensed in 2009 only for girls and women ages 10-25 [10]. One of the reasons for these discrepancies is that the vaccines have initially or only been studied in women. Clinical trials of the efficacy of the quadrivalent HPV vaccine in boys and men were still being conducted when the vaccine was first licensed for girls and women [3], and the bivalent vaccine has not been studied in men [8].

This lag may be due to the fact that questions remain about whether it is cost-effective to vaccinate boys and men against HPV. Mathematical modeling analyses seem to indicate that vaccination of men and boys is most cost-effective in populations in which the vaccination rate among women and girls is low [1, 14]. When the rate of vaccination is high among women and girls, the cost of vaccinating men and boys may outweigh the reduction of disease, since there should be sufficient herd immunity to protect men and boys from infection [1]. Herd immunity works both ways, however; men and boys can contribute to it, as well as reaping benefits for their own health [2, 15]. Practitioners thus should continue to recommend vaccination to everyone aged 11-26.

Disparities related to other demographic factors have also arisen. African American and Hispanic women have the highest rates of cervical cancer incidence and mortality [12], almost twice as high as the incidence and mortality rates among Caucasian women [16]. Additionally, African American and Hispanic adolescents are less likely than Caucasian adolescents to finish the HPV vaccine series [9, 11]. Men who have sex with men have a higher incidence of anal cancer than men who do not, and nearly all cases of anal cancer in this population are associated with HPV infection [7, 15]. Since the burden of disease from HPV is higher in these populations, it is important to provide education at every visit on the risks of HPV infection and the benefits of vaccination until the series is completed.

Moving Forward

Many great strides have been made to promote the HPV vaccine and incorporate it into the vaccine schedules for both sexes. Yet some stigma still surrounds the vaccine because HPV is primarily a sexually transmitted disease. One of the best ways to combat this stigma is by teaching that HPV infection has a well-established link to various cancers, that it is preventable, and that primary prevention is needed to reduce its incidence. We need to standardize acceptance of the HPV vaccine so that one day the cancers associated with HPV infection will be a distant memory.

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IMAGES OF HEALING AND LEARNING

The Patient as Text: Literary Scholarship and Medical Practice in Margaret Edson's *Wit*

Ann Henley, PhD

Margaret Edson's Pulitzer Prize-winning play, *Wit* [1], engages audiences in Dr. Vivian Bearing's experience and transition from prominent professor of seventeenth-century poetry to victim of terminal metastatic ovarian cancer, prize patient in experimental chemotherapeutic treatment, and, finally, to her death. By combining her knowledge of the procedures and personnel of the modern research hospital with the techniques of metaphysical poetry, Edson reveals, with candor and humor, unexpected parallels between the literary scholar and the medical professionals who treat her. *Wit* shows that, despite surface disparities, both disciplines use language to inhibit rather than promote communication, both avoid meaningful personal interaction, and both reduce the subject of research to object. Thus *Wit* challenges teachers of literature and medical professionals alike to assess their efficacy in conveying to students and patients the "simple human truths" that dignify life and death.

Dr. Vivian Bearing, a distinguished professor of seventeenth-century English poetry, specifically John Donne's "Holy Sonnets," learns from Dr. Harvey Kelekian, an equally distinguished oncologist, that she is suffering from stage-4 metastatic ovarian cancer. Edson draws on her own experience as an aide on an oncology/HIV-AIDS ward to lead her audience through Vivian's [2] downward spiral from diagnosis, through an experimental treatment for primary-site ovarian cancer—a protocol overseen by Dr. Jason Posner, Kelekian's oncology fellow and Vivian's former student—and, finally, to death. The unlikely combination of the realities of life and death in a modern research hospital and the paraphernalia of metaphysical poetry—religious and philosophic subject matter, paradox, witty wordplay, and far-fetched metaphors—reveals similarities between them, and the play becomes, as a result, a compelling and instructive experience for teachers of literature and medical professionals alike.

In true English-professor mode Vivian introduces the audience to the lexicon of metaphysical poetry in the play's first scene, remarking on the "*ironic significance*" of the inevitable hospital greeting, "Hi, how are you feeling today?" Wordplay helps Vivian deflect not only the "degrading" indignity of undergoing a pelvic exam at the hands of a former student [3], but also the desolation she feels when she is placed in isolation:

> I am not in isolation because I have cancer, because I have a tumor the size of a grapefruit. No. I am in isolation because I am being treated for cancer. My treatment imperils my health. Herein lies the paradox. John Donne would revel in it. I would revel in it, if he wrote a poem about it [4].

Edson's apt implementation of metaphysical devices provides both humor and clarity as Vivian works out the onerous philosophical puzzle, not of a poem, but of her own life and death.

As the title of the play suggests, though, it is metaphysical wit that gives the play, like Donne's poetry, its "salient characteristic." Prone on a cold metal stretcher for a CT scan, Vivian explains the significance of Donne's "Itchy outbreaks of far-fetched wit": "wit provides an invaluable exercise for sharpening the mental faculties, for stimulating the flash of comprehension that can only follow hours of exacting and seemingly pointless scrutiny" [5]. The monotony of weeks of inpatient chemotherapy gives Vivian more than enough hours for scrutiny, but "the flash[es] of comprehension" become increasingly revelatory as she encounters—and encounters herself in—the medical professionals who control her diminished existence.

Words, the stock-in-trade of the literary scholar, have for a lifetime been Vivian's tools for interpreting experience, for expanding the boundaries of awareness and comprehension—and for achieving prominence and power. She had become "a scholar of distinction" [6], eventually making "an immeasurable contribution to the discipline of English literature" [7]. When reduced to anonymous patient, she uses recitals of her accomplishments as antidotes to the depersonalization and dehumanization she endures at the hands of her caregivers. Vivian informs the audience, as a technician grudgingly searches for a wheelchair for her, that her dissertation was revised for publication in "a very prestigious venue" and that her book "remains an immense success." In it, she remarks, she "discuss[es] every word in exquisite detail" [8]. And in her current state as cancer victim, "acquisition of vocabulary" has become her "only defense": "I want to know what the doctors mean when they…anatomize me. And I will grant that in this particular field of endeavor they possess a more potent arsenal of terminology than I" [9].

Kelekian fires quite a volley of high-caliber medical jargon at Vivian during their first consultation—"invasive epithelial carcinoma," "target specificity," "antineoplastic"—as Vivian struggles to marshal analogic and analytical defenses from her own discipline: "'By cancer nature's changing course untrimmed'" [10]; "Anti: against. Neo: new. Plastic, to mold. Shaping. Antineoplastic. Against new shaping" [11]. It becomes evident, however, as Vivian summons reminders of her former professional prowess, that she, like her doctor, has used language, as Madeline Keaveney points out, not to inform but to obfuscate [12]. If her students were here, she thinks as she marks the tedious hours in

isolation, "if I were lecturing: How I would *perplex* them! I could work my students into a frenzy. Every ambiguity, every shifting awareness. I could draw so much from the poems.... I could be so powerful" [13]. Vivian's interactions with students, like Kelekian's with patients, have been what Daniel P. Sulmasy calls "pretexts in which to display personal prowess and control" [14] through the deployment of discipline-specific language.

Just as they are counterparts in their use of language as inhibitor, not facilitator, of communication, medical and literary professionals are counterparts also, as *Wit* demonstrates, in their "contact inhibition." Unlike the cancer cells Jason admires for their ability to "pile up, just keep replicating forever," the doctors and their patient alike avoid the kind of "tissue culture" [15] that might promote the healthy growth of human interaction and healing. Though he observes the obligatory clinical niceties, Kelekian ignores any hint of commonality between himself and Vivian. He makes no response to her comment that she is a professor "like yourself" [16]; he cuts short a brief moment of conspiratorial collegiality—he and Vivian laugh as his oncology fellows fail to observe her bald head—with a brusque, "Excellent. Keep pushing the fluids" [17]; he dismisses the gravity of being placed in isolation by advising Vivian to "think of it as a vacation" [18].

Kelekian is, however, positively genial compared to Jason, who consistently chafes under "crazy clinical rule[s]" like greeting a patient when collecting data in an isolation unit: "(*Remembering*) Oh, Jeez. Clinical. Professor Bearing. How are you feeling today?" [4]. He informs Vivian that his contact with patients is an unwelcome distraction from his cancer research:

> Jason: Wait till I get a lab of my own. If I can survive this...*fellowship*.
> Vivian: The part with the human beings.
> Jason: Everybody's got to go through it. All the great researchers.... Like we have to hold hands to discuss creatinine clearance. Just cut the crap, I say [19].

Jason's blunt admission of his distaste for human encounters will provide one of the flashes of comprehension so important in Vivian's eventual enlightenment.

Vivian's own contact inhibition has been a lifelong habit, as we see in the flashback to her student days with renowned Donne scholar Professor Evelyn Ashford. Seizing on Ashford's explanation of proper punctuation of the last line of Donne's "Death, Be Not Proud"—"And death shall be no more, *comma*, Death thou shalt die"—young Vivian exclaims that she will go back to the library, do more research, rewrite the paper. The wiser older scholar attempts to explain that "It is *not wit*, Miss Bearing. It is truth. The paper's not the point." She urges Vivian to engage with the poem as more than an intellectual puzzle: "Use your intelligence. Don't go back to the library. Go out. Enjoy

yourself with your friends." But Vivian can't see the connection between "uncompromising scholarly standards" and "simple human truth" and so, walking past the other students chatting on the lawn, she goes back to the library [20]. As uneasy as Jason with "the *fellowship*," she enters the hospital without family, without friends, visited only in a morphine dream by Professor Ashford, the isolation unit an apt metaphor for the 50 years of her life.

It is, however, in her reduction of subject of study to object—the human condition to an interesting locus of an intellectual conundrum—that Vivian most resembles her medical caretakers. Shortly after she's admitted for her first cycle of chemotherapy and as she is being scrutinized by one technician after another, Vivian remarks, "Now I know how a poem feels" [21]. Her growing awareness that she has become no more than a series of signs, an object of "obsessively detailed examination" [17], commences with Grand Rounds. As Jason bares her abdomen to the team of oncology fellows and points to the primary cancerous site and areas of suspected metastases, Vivian muses that Grand Rounds in the hospital resembles graduate seminars at the university: "With one important difference: In Grand Rounds, *they* read *me* like a book. Once I did the teaching, now I am taught" [22].

Vivian's reduction from active interpreter to passive object of scrutiny is vividly enacted in a flashback to her life as preeminent literary scholar, a scene that occurs precisely in the middle of the play. In it, Vivian, clad in hospital gowns and baseball cap, emphatically whacks her pointer against a screen as Donne's "If Poisonous Mineralls" is projected onto it—and onto Vivian, as she and the poem become one text. Not only does this scene furnish a visual image of patient as text, it also reveals the extent to which Vivian's obsession with poetry as intellectual puzzle has subsumed her interest in the "simple human truths" a carefully scrutinized text can reveal. Her lecture to her students emphasizes the way Donne's "vigorous intellect" is able to turn "eternal damnation into an intellectual game" but ignores almost completely "the larger aspects of the human experience," the tearful remorse his "sinnes black memorie" elicits in the speaker and his fervent trust in God's unfailing mercy [23].

The full recognition of herself as "the white piece of paper that bears the little black marks" comes in "my play's last scene" [24] as Vivian sits weakly in a wheelchair. The author of painstakingly researched and widely heralded literary criticism understands all too well that cancer has made her little more than the object of a study that will bring celebrity status to Kelekian and Jason when the results of the study are published. But, she reminds herself, the article "will not be about *me*, it will be about my ovaries.... What we have come to think of as *me* is... just the dust jacket" [25].

Acknowledging her decline from author to text readies Vivian for the flash of recognition that follows the "fellowship" conversation with Jason. When she hesitantly asks him,

"And what do you say when a patient is…apprehensive…frightened?" Jason assumes she's suffering from dementia and abruptly halts the conversation with a reminder to "Keep pushing the fluids." Once proud of having taught Jason, Vivian now perceives with dismay what he learned from her: "So. The young doctor, like the senior scholar, prefers research to humanity." Wishing "the young doctor would take more interest in personal contact," Vivian begins to reconstruct the times she denied her students "the touch of human kindness she now seeks" [26]. She recalls her rigid refusal to grant an extension on a paper to a student whose grandmother had died, her scathing rebuke to the student who was unable to "characterize the animating force" of a Donne sonnet. "Did I say (*tenderly*) 'You are nineteen years old. You are so young. You don't know a sonnet from a steak sandwich.' By no means" [27]. Earlier Vivian has noted that an eight-month course of cancer treatment is "highly educational": she has learned, she says, to suffer [28]. Ironically, in the process of dying she learns what her name, Vivian, might have meant: alive.

The "touch of human kindness" and Vivian's final flash of comprehension come thanks to Susie Monahan, Vivian's primary care nurse. Bringing Vivian a popsicle at four in the morning to sooth her tormented GI tract, Susie explains "before Kelekian and Jason talk to you" about the option to be "DNR"—to put in place a "do not resuscitate" order [29]. When Vivian reveals that she knows the experimental treatment has had no effect on the cancer and that she has no wish to be revived once her heart stops, Susie promises to take care of Vivian to the very end. Susie, who never studied poetry and whose brain, Vivian thinks, is as dull as her own has become, teaches Vivian that "simplicity" and "kindness," not "verbal swordplay" or "detailed scholarly analysis," are called for when one confronts life and death, not as an intriguing abstraction in the text of a poem, but as "*my* life and *my* death" [30].

And it is Susie who rescues Vivian from final indignities at the hands of the "medical engineers" [31] to whom she is merely research. Jason, coming to check Vivian's intake/output record, notices that her kidneys have failed and snatches up the phone to "CALL A CODE!" As a hall loudspeaker drones, "Code Blue, room 707," Susie rushes into the room:

> Susie: WHAT ARE YOU DOING?
> Jason: A GODDAMN CODE. GET OVER HERE!
> Susie: SHE'S DNR! (*She grabs him.*)
> Jason: (*He pushes her away.*) She's RESEARCH!

Susie desperately attempts to cancel the code, but the code team pours in, flings Vivian's inert body up to insert a board underneath, attaches a respirator, prepares the defibrillator, and administers a jolting shock. Susie thrusts the chart with Kelekian's DNR order in front of the code team head, who, intent upon resuscitating, shouts, "Hit her!"

and "*Vivian's body arches and bounces back down*." Jason, crouching on the floor where Susie has flung him, howls, "I MADE A MISTAKE!" and the code team at last pays attention to the order in Susie's hand: "Code team head: (*Reading*) Do Not Resuscitate. Kelekian. Shit." As Jason whimpers, "Oh, God. Oh, God," Susie pushes the code team away from Vivian's bed. They gather their equipment and leave the room, muttering, "It's a doctor fuck-up. What is he, a resident?" [32].

During this scene of arrogant intervention and technical overkill, Vivian steps out of the bed, slips off the baseball cap, hospital gowns, and bracelet, and moves slowly and attentively toward a light. In this final resurrection tableau, "*naked and beautiful*," she reaches for the light. Enlightened—free of disease, of modern medicine's research protocols, and of her own isolating cerebration—she painlessly traverses the brief pause, the comma, between life and death. But because Vivian's apotheosis is accompanied by Jason's profane prayer, *Wit* leaves its audience with another puzzle: Will the young doctor have the wit to comprehend, as the senior scholar does, that "the paper is not the point," that the proper object of all research is to discover and honor the human truths inherent in every text and every patient?

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6. Edson, 18.
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HISTORY OF MEDICINE

Diethylstilbestrol (DES) Pregnancy Treatment: A Promising Widely Used Therapy with Unintended Adverse Consequences

Arthur L. Herbst, MD, and Diane Anderson

Diethylstilbestrol (DES) was first synthesized in 1938 and was the first orally active nonsteroidal estrogen that could be used for human therapy [1]. At that time, endocrinology was in its infancy and this discovery was a unique and great advance. Recurrent pregnancy loss was a serious medical problem then as it is now. It was believed the problems were due to a faulty hormonal environment of the fetal-placental unit, rather than primarily to genetic causes, as we have subsequently learned. There were studies at that time indicating that compromised pregnancies had a deficient output of the hormone progesterone, and further studies conducted in the late 1940s in Boston using very crude measuring techniques suggested that this deficiency could be corrected by administering DES to the mother, which would then lead to a healthy pregnancy. These studies led to the widespread usage of the drug to prevent pregnancy loss [2-4].

The initial examination of the newborns born to mothers treated with DES during pregnancy showed no abnormalities (C. Smith, personal communication). The treatment, however, was controversial. (A unique double-blind study conducted at the University of Chicago in the early 1950s failed to show any improved pregnancy outcome with DES therapy [5]. This study, while negative, was conducted on a healthy pregnant population, which was different than the Boston Study, which was conducted on a high-risk population with a history of bleeding in pregnancy or multiple pregnancy losses.) An additional problem is that the hormone assays in the Boston Study were later found to be faulty and not to actually measure progesterone (Louis L. Engel, PhD, personal communication). It is believed that DES continued to be heavily used in the 1960s, and it has been estimated that 2 to 4 million women in the United States took DES during pregnancy [6].

Then, in the late 1960s, eight extraordinarily rare cases of clear cell adenocarcinoma (CCA) of the vagina were diagnosed and treated in women in their teens and early 20s in the Boston area [7]. No such cluster of cases in young patients had ever been seen previously. CCA of the vagina was known to be a cancer that rarely occurred even in older women. In an effort to understand the cause of this cluster, a case-control study was conducted at the Massachusetts General Hospital in 1971 that linked the appearance of these cancers to the patients' mothers having been treated with DES for pregnancy

complications or having had a history of prior miscarriages [8]. This study resulted in the Food and Drug Administration's (FDA) proscribing the use of DES for pregnancy support in 1971 [9]. To centralize data collection and to study the epidemiologic and clinical aspects of CCA of the vagina and cervix in DES-exposed young women, Dr. Robert E. Scully and I established the Registry for Research on Hormonal Transplacental Carcinogenesis in Boston in 1971 [10]. Further studies of patients with DES-associated CCA of the vagina and cervix showed that the cancers were rare among the DES-exposed, estimated to occur in about 1 per 1,000, with the average age of diagnosis being 19.0 years [11, 12].

Subsequently, DES use during pregnancy was associated with other adverse health effects in the exposed female offspring, including an increased frequency of anatomic problems in the female genital tract. These included cervicovaginal ridges, cervical hoods [13], and the underdevelopment of the cervix, all of which led to pregnancy complications including premature birth of offspring of the DES-exposed daughters [14]. Evaluations of DES-exposed daughters who did not have CCA showed a high prevalence of vaginal adenosis (benign glands in the vagina), and this finding was correlated with the time during pregnancy that the mother began DES treatment [15].Vaginal adenosis was also found to be associated with the development of vaginal CCA [16]. DES-exposed daughters were found to have abnormally shaped uteri, which led both to infertility problems and premature births of their offspring [17, 18]. Additional follow-up of DES-exposed mothers and daughters showed that each group appeared to have an increased risk of developing breast cancer [19-22].

Most recently, National Cancer Institute (NCI) collaborative studies showed that in-utero exposure of women to DES is associated with a high lifetime risk of a broad spectrum of adverse health outcomes, including an increased risk of breast cancer in daughters 40 years of age and older [22]. For DES-exposed sons, an increased risk of cancer has not been demonstrated [23] but they do have increased prevalence of maldescent of the testes, epididymal cysts, hypotrophic testes, and varicoceles [24-27]. This unique population continues to be studied long-term in a multi-institutional study by the National Cancer Institute, both to monitor the possible adverse health effects of DES in this population and to clarify which potential adverse effects are statistically significant and therefore of increased medical concern in this population. Some areas of concern include possible increased rates of cancers other than those cited previously, autoimmune diseases, and cardiac problems [28].

The DES granddaughters (third generation) are also being studied, and initial results showed that exposed granddaughters started their menstrual periods at a later age and were more likely to have irregular cycles than their unexposed peers, but they reported similar reproductive outcomes [29]. Thus far no other adverse health events have been demonstrated in this group. Regarding third generation DES-exposed sons, some studies

have suggested an increased risk of hypospadias, a finding which has not been confirmed in subsequent studies [30, 31].

The CCA cases are currently being evaluated at the Registry for Research on Hormonal Transplacental Carcinogenesis. This registry, initially established in Boston [10], is now housed at the University of Chicago. Cases being accessioned are all cases of CCA of the vagina and cervix diagnosed in women born since 1948, whether or not there is a history of in-utero DES exposure. Thus far, more than 700 cases have been accessioned. Cases diagnosed at an early stage have been cured but cases diagnosed at a late stage have usually been fatal. About two-thirds of the cases have a history of exposure to DES [32] and most have developed in women under the age of 30 years, but the cancers are still occurring in older DES-exposed women, the oldest of whom was 62 years of age at the time of diagnosis. In addition, all cases of adenocarcinoma of the fallopian tube occurring in DES-exposed daughters are being accessioned.

This is a tragic example of a therapy that looked promising and was based on the best (but faulty) scientific evidence available at the time, which led to the widespread use of a treatment that the physician anticipated would help the patient have a successful pregnancy. However, due to the sensitivity of the developing fetus to an externally administered artificial hormone, unanticipated and severely adverse consequences developed. The physicians who prescribed DES were following what appeared to be accepted medical therapy that was based on published studies. Unfortunately, these studies were not based on the type of rigorous evaluation that is available today. There is still a risk of prescribing treatments that anecdotally appear promising but are not scientifically proven. This is a particular risk among infertility patients and obstetrical patients due to the "need" to have a positive outcome. The DES saga, in the opinion of the authors, provides a strong reason to support the use of carefully constructed scientific trials to evaluate new therapies, and this admonition is particularly applicable to the pregnant patient, since the fetus is often more sensitive than the living offspring to outside influences.

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Suggested Readings and Resources

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