

## Ethical issues in cancer genetics

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#### Abstract

The history of medical ethics has provided, at various junctures, focus on major principles such as justice, fidelity, autonomy, beneficence, etc. When deontological (rule-based) perspectives received competition from utilitarian (results-based) methods of analysis in the 19th century, changes in emphasis helped pave the way for ethical assessment of the Darwinian, Mendelian, Freudian and Einsteinian revolutions. Modern frameworks in medical ethics have returned to principlism (which has its roots in the ancient Greek philosophical tradition that directs our attention to the Good, the True and the Beautiful). This in turn has conditioned much of the underpinning of genetics counseling, with emphases on justice, beneficence and autonomy. The recent opening up of oncogenetics offers an opportunity to revisit the insights of the past and refine them for clinical oncology settings. There are important problems and issues which arise in several contexts: intrafamilial dynamics, economic concerns, professional qualifications, research settings, and most recently reproductive decision-making.

#### Introduction

As modern scientific insights deepen and strengthen our abilities to discover and apply knowledge of the fundamental biological processes involved in malignant neoplasia, there is a concurrent need for us to mine the humanistic and philosophical meaning of the cancer experience and its social context. This essay will explore some philosophical and theological foundations, and modern applications, of medical ethics. The descriptive aspects of oncogenetics (e.g. tumor-suppressor genes, proto-oncogenes, DNA mismatch repair genes, autosomal dominant inheritance patterns with incomplete penetrance and variable expressivity, genetic heterogeneity) are

discussed elsewhere in the encyclopedia, and a basic knowledge of those scientific materials is presumed in this treatment.

## **Historical overview of ethics**

Ethics is the systematic study of norms and practices governing interactions between persons, who are moral agents with rights and obligations. The ethicist asks how people should act. While it may seem ideal to articulate timeless answers to these questions, the process of addressing them is usually conditioned by cultural and social context of the inquiring philosopher, so that practical results typically are expressed in ways that reflect the religious traditions and foundational assumptions of the writer.

The roots of modern ethics can be traced to early religious traditions that began to take form in written documents nearly 3000 years ago. During what has been called the “axial age”, a relatively short period of several centuries, leading thinkers independently reached very similar new insights regarding the role of the human agent, the conscience, and the notions of duty, honor and responsibility. They rejected the animistic magical explanation of events and the notion that divine agencies are capricious or vindictive. They promoted the notion that individuals are obliged to maintain a relationship axis by which they experience and participate in creativity and righteousness. Thus the Hebrew prophets (Isaiah, ca. 770-685 BC; Micah, ca. 760-700; Jeremiah, ca. 650-580 BC; Ezekiel, ca. 620-570 BC, etc.) in the Mediterranean basin, Siddhartha Gautama (ca. 563-483 BC) in the Indian subcontinent, and Han Fei-Tzu (ca. 551-483 BC) in China expressed convergent ideas without having had any opportunity to know of each others’ teachings.

Soon thereafter, in another region of the Mediterranean basin, Socrates (ca. 470-399 BC), his student Plato (429-347 BC), and his student Aristotle (384-322 BC) developed strong intellectual foundations for ethical thinking, probably without having any awareness of the teachings of those earlier thinkers. The more religiously motivated teachings of Jesus (ca. 4 BC-29 AD) and Mohammad (570-632 AD) were founded largely on the same cultural tradition to which Isaiah and the other Hebrew prophets had made their contributions. As Europe languished in relative intellectual quiescence, the Islamists preserved and treasured ancient Greek philosophical writings. Then, while their culture was slipping into fundamentalism, Aristotle’s works were “rediscovered”. The Jewish scholar/scientist/physician Moses Maimonides (1135-1204) conducted seminal study and reflection on these materials. A conscious and systematic effort to incorporate them into a Christian hermeneutic was undertaken by several people at about that time, most importantly Thomas Aquinas (1225-1274). He and Maimonides were, however, still unaware of the Buddhist and Confucian lines of thought.

Rene Descartes (1596-1650) posited, as a starting point in his search for a reliable method in moral philosophy, that all persons believe themselves to enter every debate with an adequate deposit of common sense. In other words, we can and should assume that on entering any debate, each participant begins with good will and an interest in reaching a well reasoned and “correct” conclusion. When we find this difficult to achieve, he believes, it is not due to ill will or poor motivation, but rather to differences in perspective. A modern reader might be tempted to think that Descartes was expressing cynicism, but apparently he took this presupposition seriously. It is intriguing to contemplate how different much human discourse might

be if we all genuinely and habitually employed this as a starting point for familial, professional and political interactions!

Immanuel Kant (1724-1804) is the supreme adherent to deontology, the normative ethical framework which is based on adherence to universal rules of behavior, often received as religious revelation or dogma. He perceived two things that consistently inspire awe and respect: the starry heavens above, and the moral law within. He derived for us the “categorical imperative” whereby a moral agent should never engage in any activity unless s/he is convinced that all moral agents should always choose the same course of action. This lofty expectation is, of course, not lightly achieved. Yet none of the serious thinkers in religious or philosophical arenas has ever offered us easy virtue. Plato’s eternal search for the Good, True and Beautiful is always demanding. Gautama Buddha requires that the yogin, having achieved enlightenment, return from blissful contemplation to the marketplace and manifest compassion on others by teaching them to enjoy the same accomplishment. Jesus demands self-sacrificial love. Mohammad mandates inclusiveness and a radical option for the poor and oppressed.

Nineteenth century utilitarianism incorporated into the mainstream of ethical dialogue some of the practical religious thinking embodied in the tradition of “casuistry” that had been employed by 17th and 18th century Jesuits (an order of Roman Catholic priests famed for scholarship) to meet the challenges of the confessional. Casuistry has to do with discerning probable, but not always certain, approximations of virtue in the application of ethical principles to daily ongoing decision-making. The utilitarians evolved an ethical analysis in which the greatest good for the greatest number became the ruling principle. Seeking the greatest pleasure and the least pain (not for the agent personally [hedonism], but for the whole population of those involved in the decision and its outcomes) became the normative heuristic. Out of this emerged the notion that the ends might justify the means, a formula that is not attractive to most deontologists. However, consistent utilitarianism also makes demands on the individual, who may be called upon for great personal sacrifice. Popular 20th century American culture found this expressed dramatically and explicitly in Mr. Spock’s suicidal actions to save the entire crew of the Enterprise in the movie Star Trek II: Revenge of Khan. It has, however, long been part of the high lore of warfare and chivalry, whenever one soldier lays down his life to preserve the lives of his comrades.

A broadly based perspective that can take advantage of all these traditions was possible only in the past century, when syncretistic approaches to diverse cultural traditions could be achieved as a result of improved transportation and communication. Albert Schweitzer (1874-1964), a giant of theological and scientific scholarship as well as professional and personal sacrifice, proposed an overall ethic of reverence for life that sought to incorporate the strengths of a wide variety of preceding thinkers. Syncretism always hazards being criticized for failing to adhere to or achieve the highest purity in any given system of thought. Twentieth century popes, theologians, and philosophers of many religious and secular schools, and sincere secular-minded practitioners of health care with strong interest in seeking the Good, have elaborated a broad and deep literature addressing the challenges of ethics in a world imbued with techno-scientific instruments and opportunities. Many of them strive to avoid any attenuation of their specific cultural and religious contexts in that process.

Principlism has offered, in this context, a modern reconsideration of normative ethical foundations applied to apparently new problems posed by technology. The

mantra of the principalist is “beneficence, non-maleficence, justice and respect for autonomy (the right to know about one’s risk factors, and the right not to know things that one prefers not to address)”. This heuristic has achieved broad acceptance in the community engaged in “bioethics”. These four pillars for ethical analysis have found an important application in genetic counseling, a paramedical profession which arose during the third quarter of the century and which is focused on genetic decision making processes. Today most professionals engaged in genetic counseling are masters-level people with training in both psychosocial fields and applied genetics; most others are medical geneticists (most MD, some PhD, some both).

## **Counseling**

Someone once noted facetiously that genetic counseling has been with us as long as there have been in-laws anxious to assert “that never happened in our family.” The more subtle, and so more readily overlooked, errors in application of science to human challenges will often take a form such as “the risk is only 6%, so you should not waste any sleep over it.” If the empiric risk for some adverse event is “only 6%”, the meaning (medical, social, psychological, spiritual) for the person at risk remains a function of the relative impact of the problem in question. A 6% risk for a fractured finger is not equivalent to a 6% risk for metastatic ovarian tumor. A 6% risk for male breast cancer associated with carrier status of a mutation in the BRCA2 gene may be a matter of great concern because such tumors often blind-side the patient who assumes his risk to be essentially zero, so that he may have advanced disease before appreciating a need for medical attention.

Consequently, effective genetic counseling must not only quote the most scientifically based risk factors and explain the technical aspects of heredity, but also travel the notoriously complex passages of self-image, religious conviction, social obligation, and reproductive goals. All of these can inhabit the psyche of the person at risk for (or already affected by) such a distressing health problem as cancer. The effective genetic counselor knows of all these hazards and develops the skills to assist patients in navigating the troubled waters between them. Always and everywhere, the genetic counselor maintains the self-discipline to avoid directing the decisions to those that might best manifest his or her worldview, helping the patient to express personal perspective and values in the process. The question “What would you do in my situation?” is consistently met with the response “I do not know, but let us explore how you might express your own views and needs in a decision that fits your life.” Few physicians and nurses have had the training opportunities to develop this peculiar skill, which is central to the training of the genetic counselor and helps define that specific profession. It also requires serious investment of time for the conversation, so that it can occur in the full context of explicitly appreciating the patient’s courage in facing the challenges involved.

Avoiding directiveness in genetic counseling is motivated by dedication to the principle of autonomy, but it represents a utilitarian bias because it eschews adherence to any pre-existing dictum or moral rule by which decisions must be reached. So, a deontologist finds it difficult to provide genetic counseling in the form that most modern medical professionals have learned to perceive it. The closest most geneticists will allow ourselves to come to directives and deontologic paradigms is that we will not perform any action that appears to us to be malevolent or unjust. For example, seldom will we agree to test minors for conditions that have late adult onset

and lack preventive strategies. Further, we are fairly strict in following protocols for consultation and testing. For example, an unaffected person concerned about risk for inheriting mutations in BRCA1 or BRCA2 will be urged to first engage an affected relative in the process, to maximize the chance of identifying a specific mutation in the family, but also minimize the risk that the affected person might later learn of risk factors that s/he preferred not to address. Thus, we always approach the issues at hand as being familial rather than only individual matters; this has the advantage of building a communal context for the conversation, but the dangers of being embroiled in long-standing familial disputes.

## **Family dynamics**

A woman with a strong personal and family history of breast and/or ovarian cancer, who has already undergone bilateral mastectomy and/or oophorectomy to manage her personal risks, will sometimes present for genetic counseling and testing in order to provide useful information to her daughter, sister, or other relative at risk of inheriting the same predisposing mutation (if, in fact, such a mutation is demonstrable). The genetics professional, having noticed that her personal management has been well directed and thorough, does not repel her questions, but honors her stated interests. Meanwhile, s/he makes it a habit to focus first on the patient's own medical care, and then derivatively on the potential benefits to those beloved relatives. Thus beneficence and justice are honored along with respect for autonomy.

The core material of all ethical discourse is interpersonal relationships. This has been paradigmatic since the axial age, when the early sages taught that the quality of relations among persons is the foundation of upright living, and reflects the stance an individual assumes before a loving but demanding deity. It is not surprising, then, that genetic counseling for cancer risk factors is directed often and intently on intrafamilial communication. Principlism can be encountered as a bland recitation of four intuitively apparent truths about human interaction, but in the pursuit of one principle the counselor sometimes encounters collisions with the others.

Personal autonomy enshrines the right of the individual to ask questions for whatever reason she wishes (as noted above), and also to keep confidential the fact that s/he carries a deleterious mutation posing high probability of tumorigenesis. However, the principle of justice motivates informing relatives who are at risk for inheriting the same factor. Counselors sometimes experience moral dissonance. As a prime example, a proband may refuse to contact, or to grant permission for others to contact, relatives with whom s/he has been at odds over a family dispute. The path of wisdom is not always evident to the casual observer, but it is essential to find a balance between nondirectiveness on the one hand and an instinctive sense of obligation to invite an anger-harboring consultand to contemplate the larger contexts of benevolence. In their monumental documentation of geneticists' attitudes around the world, Wertz and Fletcher (2004) surveyed many hundreds of practicing medical geneticists and genetics counselors in 36 countries. They found (pp. 54 and 393) that 47% of American respondents would respect autonomy in the setting of a mutation for Li-Fraumeni cancer-family syndrome and remain silent, while 30% would divulge to at-risk relatives without permission of the proband if asked, and 12% even if not asked. Worldwide, the results were 36%, 32% and 17%, respectively.

Genetic counseling then overlaps with psychological counseling, as the notions of forgiveness and the healing of relationships become a part of the discussion that began with explanation of the technical significance of frame-shift mutations and probabilistic analysis of variable expressivity with incomplete phenotypic penetrance. So we learn to uphold and acknowledgement the patient's suffering, insight and foresight, generosity and creativity in seeking knowledge that may better inform her own care and also the decisions faced by her relatives.

Another challenge in this arena arises when familial relations are strained in regard to the desire to investigate risk factors. A woman anxious to know her status for an important mutation that has been documented in her maternal aunt may find that her mother (who biologically attaches her to that aunt) wants nothing to do with genetic testing. If the consultand is tested and found to harbor the mutation, its route to her must have passed through her non-consenting mother, whose blindness to the testing outcome is almost impossible to achieve if the two have any contact. So the daughter's autonomy violates the mother's and an injustice is perpetrated.

A woman preparing to determine whether she carries a predisposing mutation, having grasped the importance of alerting the extended family to the risk factor, asked what she ought to do about a cousin who is not actually at risk since he was adopted...but does not know this detail of his own origins and so presumes himself to be at risk. This is, of course, a special case of the broader problem of non-paternity which is sometimes inadvertently exposed when extended families are subjected to genetic testing in the pursuit of risk factors. Aside from leaving him to continue behaving as though his risk is elevated, it is difficult to discern what course of action could be chosen justly and beneficently but still honor his autonomy.

Personal autonomy (the right to know about one's risk factors, and the right not to know things that one prefers not to address), the demands of justice, the allure of beneficence, all converge in this arena and challenge the counselor who confronts hard realities of individuals with psychosocial difficulties, and families broken by old wounds. Thus, directiveness prevails in our custom of arguing vigorously for communication with at-risk relatives when a person has learned of a mutation but expressed disinclination to advise siblings or others who are clearly at risk. We do this in the hope of escaping the conflict of simultaneous dedication to the principles of autonomy and justice.

## **Economics**

In venues that do not have universal health care coverage as a right of citizenship, the cost of molecular testing in search of mutations that place their carriers at high risk for malignancy is very significant. Even when universal coverage is afforded, this may be adumbrated by policy decisions which set the bar fairly high for determining eligibility.

The problem is exacerbated in those situations which involve patents or other proprietary aspects of the testing process. The ethical debate over appropriateness of patenting human genes or the processes for testing them is not addressed in this essay, but is clearly worthy of considerable attention; the present author considers such patents highly inappropriate and contrary to the public good.

Significant efforts are sometimes demanded, from patients and caregivers, to secure authorization under third party (insurance) payers. Absent reliable insurance coverage of some kind, or unusual disposable income that obviates concern about

cost, there are important economic barriers to seeking the presumably useful information that may be available in the laboratory. Every time such a barrier exists, it constitutes a violation of the foundational ethical principle of justice, since it prevents access of the poor to benefits of technology enjoyed by the well endowed. Overcoming such injustice has innumerable practical as well as theoretical challenges, but no ethical analysis is complete without acknowledging this problem. Such problems are not specific to cancer genetics, however, but are found in every aspect of health care. Indeed, distributive justice is an arena of concern in all settings where there are populations or individuals facing disadvantage in enjoyment of the world's resources.

## **Professionalism**

As in any highly specialized area of medical practice, consultations for discussion and testing pertaining to genetic risk factors associated with high probability of developing cancer should be undertaken only by persons who have a thorough background in the field, and also the ability to maintain familiarity with ongoing changes in that field. Change and growth of pertinent materials in this area are unusually rapid. Consequently, such consultations should not be undertaken by general practitioners, just as one would not wish to have an appendectomy or cesarean section performed by someone who only has occasion to do them once or twice annually.

Board certification by national or regional examination, with appropriate continuing education, should be considered essential. A specialist in clinical genetics, working with a nurse or counselor with expertise in genetics or oncology or both, should be considered the highest standard. A counselor or nurse with genetics credentials, collaborating with an oncologist, would be the next best. Accepting less might flirt with the principles of non-maleficence and justice, whereby professionals have a duty to provide the best reasonably possible care; in this setting that calls for a high level of familiarity with the field and its ongoing developments.

There are several reasons for the above perspective. One is the importance of thorough and insightful documentation of family history; without a background in genetics, many would overlook the significance of an endometrial tumor in a member of a family with several cases of colon carcinoma. Another is the adequate preparation of the patient for testing, since a wide range of emotional states may accompany results which reveal elevated personal health risks and/or material that should be communicated to relatives. Yet another is the complexity of the testing itself, and the delicacy of explaining test results when they are confusing, technically complex, or anxiety-provoking.

Such considerations revolve around the fact that genetic tests for cancer predisposition are highly complex not only in terms of laboratory expertise (as reflected by their high cost) but also in terms of their impact on the patient and the patient's family. Thus the preparation for these tests is proportionately more painstaking, whereas a routine blood count, or monitoring serum level of antibiotics or anticonvulsants, calls for very little advance discussion.

## **Research**

The usual issues of informed consent apply to this field of investigation, as do the usual safeguards of privacy and of guarded access to results that have not been certified by a licensed clinical laboratory. The special case of inadvertent exposure of non-paternity is vexing but has already been considered in other genetics arenas. Ethical issues that pertain specially to cancer genetics research are not numerous. It is difficult to imagine, for example, any committee for the protection of human subjects to allow any genetics research to interfere with or postpone appropriate therapeutic interventions.

Existing literature and ongoing debate about the use of archived specimens applies in the cancer genetics arena, but this arena does not introduce new ethical concerns that are not already under consideration from other avenues of discussion.

Probably the greatest danger of inappropriate professional action in the cancer-genetics field is the premature release of new information which might mislead the general public about availability of predictive, diagnostic, or therapeutic modalities based on molecular genetic factors. Again, however, this is not unique to cancer genetics.

## **Reproductive decisions**

Many middle-aged and elderly persons are seen for consultation and testing to determine whether a predisposing mutation is associated with their tumors. Often they express their interest as being motivated by concern for clarification of risk factors facing their sons and daughters (though the clinician's first interest must always be the utility of this kind of information to guide treatment and surveillance decisions for the patient him/herself).

When those offspring learn that they have 50% risk of having inherited a genetic risk factor, or when the proband is a person still in the reproductive age range, one encounters the opportunity to apply the new information to decisions about child bearing. Some people faced with such materials will opt to forego offspring; some might turn to gamete "donors" and/or surrogate parents. Few will give serious consideration to termination of pregnancy after prenatal diagnosis of transmission of the mutation (since such a termination involves an otherwise presumably normal fetus whose risk for ill health is remote and poorly defined). Some who have the resources and the motivation might employ in vitro fertilization followed by preimplantation genetic diagnosis so that only embryos lacking the mutation are transferred; this cleanly moves around the problem of termination for many people concerned about maximizing the health of future children, but it still opens the window on potential abuse of technology for election of traits that have nothing to do with disease risks ("designer babies").

Personal autonomy, which is always a central concern in seeking informed consent for testing and for treatment, is especially important when reproductive decisions are at issue. The beneficent practice of medicine might motivate professionals to guide patients into decisions deemed of higher moral content by the professional, but genetic counseling has a consistent emphasis on autonomy as the overarching principle in such settings. This emphasis beckons us into troubling territory when families elect to test a pregnancy for mutations that pose an increased risk for cancer in the fourth and fifth decades of life;

All of these considerations are highly personal and sensitive. They open the entire field of potentially controversial use of high technology and seeking to control health

risks by selecting genetic features in planned offspring. This does not absolve professionals working in the cancer genetics arena from introducing patients to the questions and working with them to achieve answers compatible with their values and goals. In fact, the delicacy of this material highlights the importance of all the other ethics concerns in cancer genetics being treated with respect.

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