Ethical Issues: Overview in Genomic Analysis and Clinical Context

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Abstract

This chapter discusses ethical, legal, and social issues (ELSI) centered around hereditary breast and ovarian cancer syndrome (HBOC). In the first half, we discuss ethical considerations in the context of decision-making on genetic testing, debates on incidental/secondary findings (IFs/SFs), and global trends in clinical and/or genetic data sharing, including with patients and their family members. In the second half, from the perspective of clinical ethics of cancer diagnosis and treatment, we introduce the importance of decision-making and care based on the shared decision-making (SDM) approach and practical points in prophylactic surgery. We also discuss dilemmas that arise regarding confidentiality between medical professionals and their patients. This includes disclosure of genetic information with genetic relatives, and challenges in family communication, in which carefully assessed and encouraging support may be needed for patients and family members.

Keywords

Ethical, legal, and social issues (ELSI) · Bioethics · Medical ethics · The right to know/not to know · Shared decision-making (SDM) · Prophylactic surgery Family communication · Incidental findings/secondary findings (IFs/SFs) · Data sharing · Confidentiality

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17.1 Introduction: Genomic Medicine/Research and Ethical Issues

From an ethical perspective, genetic and genomic analyses may evoke certain dilemmas, since genetic data are characterized such that they are partially shared among genetic relatives, for not only the diagnosis of current health conditions but also the assessment of future disease risk among individuals. Although "respect for autonomy" is one of the fundamental principles in medical ethics,[1] potential conflicts of interest exist between patients and their family members. Furthermore, diagnosis, treatment, and prevention options may highly influence personal life plans, and various values may depend on individuals, cultural/social context, and historical backgrounds. Multidisciplinary collaborations are required to unravel such questions with no correct answers. Indeed, genetic/genomic studies have always promoted the ethical and psychosocial viewpoint.

The Human Genome Project (HGP) was a remarkable achievement by international collaboration groups from 1990 to 2003, which aimed to determine the complete sequence of the human genome at nucleotide-level resolution. The US Department of Energy (DOE) and National Institutes of Health (NIH) devoted 3–5% of their annual HGP budgets toward studies on ethical, legal, and social issues (ELSI) [1], which consider the policies and examine the implications of genomic analysis technology with respect to individuals, families, and communities. Such studies include various issues, i.e., fairness in the use of genetic data among insurers, employers, and courts; privacy and confidentiality issues; psychological impacts; and stigmatization owing to an individual's genetic differences and reproductive issues. Furthermore, the NIH National Human Genome Research Institute (NHGRI) continued to fund the ELSI program [2].

Today, over 30 years have elapsed since the initiation of the HGP, and genetic testing and genome sequencing have become increasingly popular in basic research and the clinical setting. Although the basic ELSI remains unchanged, numerous technological advantages and changes in the social environment have been brought about. In this chapter, highlighting our research results conducted in Japan, we overview several ethical topics surrounding HBOC (hereditary breast and ovarian cancer) from research and clinical perspectives.

[1] Four ethical principles of medical ethics consisting of "respect for autonomy," "beneficence," "non-maleficence," and "justice," which were advocated by T. L. Beauchamp and J. F. Childress in their book *Principles of Biomedical Ethics* in 1979 (Beauchamp TL and Childress JF. Principles of biomedical ethics. New York: Oxford University Press; 1979.) After decades, although these traditional principles were updated by numerous researchers, their framework still seems applicable to present medicine because of their simplicity and practicality, including genetic and genomic medicine.

17.1.1 The Right to Know/the Right Not to Know: A Basic Ethical Principle in Genetic/Genomic Analysis

Individuals undergoing genetic testing not only have "the right to know" but also "the right not to know" his/her genetic information. This concept is derived from an argument in the 1990s by Dr. Nancy Wexler, who had been at risk of Huntington's disease (HD; a progressive brain disorder without definitive treatment) and had contributed to the assessment of the predisposition to HD on the basis of the *HTT* gene. The great success of Wexler and her colleagues in detecting *HTT* gene facilitated the diagnosis of patients and the prediction of future risk of HD among asymptomatic individuals [3]. There was a debate as to whether at-risk individuals had the "duty to know" their carrier states [4, 5]. Wexler insisted that patients and their family members had the right not to undergo genetic testing, and presymptomatic genetic testing should be accompanied by a careful genetic counseling process with trained counselors [6, 7].

At that time, this discussion also influenced the rules and ethical issues regarding disorders with early onset and with potential preventive and treatment strategies. For instance, the American Society of Human Genetics (ASHG) recommended that predictive genetic testing for hereditary breast and ovarian cancer syndrome (HBOC) and career testing for cystic fibrosis (CF) should be voluntary, with appropriate education and counseling [8, 9].

As one of the global consensuses, *The Universal Declaration on the Human Genome and Human Rights* (1997) of the UNESCO stated the following: "(c) The right of each individual to decide whether or not to be informed of the results of genetic examination and the resulting consequences should be respected" (B. Rights of the persons concerned, Article 5), with the emphasis on respecting human dignity regardless of genetic characteristics [10]. The same principles were included in the *Convention on Human Rights and Biomedicine* by the Council of Europe [11], and the *International Declaration on Human Genetic Data* (2003) by UNESCO confirmed "the right to decide whether or not to be informed" [12].

After the several decades, the germline *BRCA* variant is considered a medically "actionable" finding, i.e., "there is a recognized therapeutic or preventive intervention or other available actions that have the potential to change the clinical course of a disease or condition" [13], or "druggable" for molecular-targeted drugs including PARP (poly(ADP)-ribose polymerase) inhibitors.

Certainly, *BRCA* is a medically actionable variant; hence, it is crucial to carefully assess and balance both risks and benefits of genetic testing of individuals.[2] While

[2] For instance, the US Preventive Services Task Force (USPSTF) revised its recommendation statement on *BRCA*-Related Cancer: Risk Assessment, Genetic Counseling, and Genetic Testing in August 2018: They concluded that with moderate certainty, the net benefits of risk assessment, genetic counseling, and genetic testing outweigh the harms among women whose family or personal history is associated with an increased risk for *BRCA1/2*variants, while the harms outweigh

undergoing genetic testing may relieve a woman's anxiety and uncertainty about whether she has a hereditary cancer risk, especially those with a strong fear for developing cancer, studies have reported that *BRCA*-positive women without a cancer diagnosis may experience long-term uncertainty [14, 15]. A longitudinal study from the life course perspective (LCP) showed how lives were changed among women after knowing that they carried *BRCA* variant, and different emphases on concepts have emerged across different age groups (i.e., 20s, 30s, 40–50s) [16]. A large, prospective analysis performed in 2008–2012 in the USA revealed that nearly one-third of patients did not pursue *BRCA* genetic testing after genetic counseling, with insurance coverage and out-of-pocket cost concerns being the top nonmedical reasons for declining the test [17].

Furthermore, since HBOC is often recognized as a "women's disease," the diagnosis of breast or prostate cancer among male at-risk persons or patients may be confounding or be met with low interest toward such information.

17.1.2 Shared Decision-Making Model: Collaboration of Medical Professionals and Patients for Better Decision-Making

What would be the most effective approach to support the decision-making of patients on matters that significantly affect their way of life?

Shared decision-making (SDM) is a model of decision-making in clinical practice for procedures such as genetic testing [18]. SDM is characterized by having at least both the physician and patient involved in the decision-making process and having both parties share information, take steps to build a consensus, and reach agreement [19]. Of course, one physician and one patient is the most simplified model of SDM. In practice multiple physicians may be included or consulted, and the patient may include or consult with his/her family, friends, counselors, and nurses [20].

In general, informed consent (IC) is aimed at allowing patients or clients to decide whether to consent or dissent (reject) after receiving a complete explanation and understanding of the best-possible treatment plan, as deemed by the clinician. However, SDM emphasizes the process of consensus building wherein the clinician and patient or client collaborate and share information. In this bidirectional process, the clinician provides all potential options from the medical perspective, while the patient shares thoughts on the effect of the illness and treatment on his or her life and cherished values. Although IC and SDM have numerous similarities, IC is a clinician-centered process wherein the patient is relatively passive, whereas SDM requires collaboration between the clinician and patient in decision-making. That is,

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the benefits among women whose family or personal history is not associated with an increased risk (U.S. Preventive Services Task Force (USPSTF). *BRCA*-Related Cancer: Risk Assessment, Genetic Counseling, and Genetic Testing. In: Recommendation Topics. 2019. https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/brca-related-cancer-risk-assessment-genetic-counseling-and-genetic-testing. Accessed 15 Feb 2021)

the concept of SDM is consistent with the "interpretive" or "deliberative" models, which are situated in-between the "paternalistic" and "informative," in the four models of the physician-patient relationships advocated by Emanuel and Emanuel [21, 22].

SDM is particularly important in a situation with high uncertainty (i.e., lack of clear evidence regarding the best-possible outcomes) and variability in patient values and preferences [23]. It was suggested that SDM would help women make decisions about *BRCA* genetic testing, cancer prevention, and treatment decisions, as there is no single correct plan [24]. As in "anticipatory guidance" in genetic counseling, SDM requires the clinician and patient to collaborate in making the best-possible life plan by considering the potential positive and negative effects of genetic testing, work (employment), marriage plans, plans on conceiving children, and relationships with relatives. Some tools called decision aids (DAs) are used to support an individual in making a shared and informed decision about *BRCA* testing and to clarify values and preferences [25].

17.1.3 Incidental/Secondary Findings (IFs/SFs)

Genomic analysis involving next-generation sequencing (NGS) approaches has been widely introduced in the clinical setting. This technology helps determine the sequence of DNA more rapidly and at a lower cost than conventional Sanger sequencing, and it is used for analyzing panels of multiple genes, exomes, and whole genomes. One of the controversial issues is the management of "incidental findings (IFs)" or "secondary findings (SFs)."

This issue was originally derived from a discussion on whether researchers have a duty to disclose an unexpected finding to research participants of a study, using structural magnetic resonance imaging (MRI) of the brain or computed tomography (CT) colonography, and the discussion extended to the field of genomic research [26, 27]. Wolf et al. defined an IF as a "finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study" [28] and led the controversial debates. Since NGS has been widely used in the clinical setting, the discussion also applies to a medical professional's duty to patient and family.

The American College of Medical Genetics and Genomics (ACMG) issued the first clinical recommendations for the return of IFs from whole-genome/whole-exome sequencing and provided a list of a minimum of 56 genes associated with 24 health conditions, which would be extensively screened clinically and reported to the attending physicians, irrespective of the patient's preference [29]. This recommendation emerged controversial, especially regarding mandatory analysis and infringement of the patient's autonomy [30]; consequently, ACMG updated the recommendation that patients should be able to opt out of the analysis of genes unrelated to the indication for testing during the obtainment of informed consent [31].

After the ACMG recommendation and related controversies, the US Presidential Commission for the Study of Bioethical Issues (PCSBI) issued a report called

ANTICIPATE and COMMUNICATE: Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts in 2013 [32]. The report verified the taxonomy of IFs/SFs and provided context-specified recommendations for their management in the clinical setting, basic research, and direct-to-consumer (DTC) genetic testing. While the "primary findings" are the results obtained as the primary target of a test or procedure, IFs and SFs are the results that are obtained outside of the original purpose. IFs are unintended discoveries, which can be categorized as "anticipatable" or "unanticipatable" IFs, considering the current state of scientific knowledge. In contrast, SFs refer to a finding which is actively and intendedly sought by a practitioner but is not the primary finding. Furthermore, PCSBI reflects a clinician's ethical and professional responsibilities as to the following points: informed consent, to convey clearly to patients the possibility of discovering IFs/SFs and communicate with their patients regarding follow-up alternatives; shared decision-making, to encourage patients to ask questions, state reservations, and express preferences about the return and management of IFs/SFs; clear communication, to consider incorporating graphs and other visual displays to enhance patient comprehension of risk in medical decision-making; and clinical judgment, to minimize the likelihood of IFs through communication with patients to better understand symptoms and help narrow the list of potential diagnoses [33]. Table 17.1 summarizes the classification of IFs/SFs by the PCSBI, along with suitable examples, which we modified.

Table 17.1 Classification of incidental findings/secondary findings

Type of result discovered	Primary finding	Incidental finding: anticipatable	Incidental finding: unanticipatable	Secondary finding
Description	Practitioner aims to discover A, and result is relevant to A	Practitioner aims to discover A, but learns B, a result known to be associated with the test or procedure at the time it takes place	Practitioner aims to discover A, but learns C, a result not known to be associated with the test or procedure at the time it takes place	Practitioner aims to discover A and also actively seeks D per expert recommendation
Examples	Obtaining positive findings for *BRCA* variants after conducting diagnostic or presymptomatic genetic testing for *BRCA*	Discovering brain tumor when conducting magnetic resonance imaging (MRI)	DTC genetic testing company identifying genetic variants that are not currently associated with the disease	Detecting possibility of germline variants which ACMG recommends that any laboratories conducting genome sequence in clinical purpose should actively screen

See p. 27 in [32]; "Examples" were modified by authors

ACMG revised the terminology to "secondary findings" since the updating of the policy statement in 2016 (ACMG SF v2.0) because the enlisted genes are intentionally being analyzed, as opposed to genetic variants found incidentally or accidentally [34]. ACMG released an updated policy statement and minimum list for reporting of secondary findings (SF v3.0), which include 73 genes in May 2021, and the working group noted its plan to update the list annually [35–37].

In clinical oncology, such genomic analysis may lead to identification of inherited susceptibility to cancer or other diseases through either somatic mutation profiling or germline multigene (multiplex) panel testing, which is also referred to as "germline findings" instead of "incidental" or "secondary findings."

The updated *Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility* (2015) of the American Society of Clinical Oncology (ASCO) [38] requires oncology practitioners to communicate the potential for incidental and secondary germline information to patients before conducting somatic mutation profiling (genomic tumor profiling test) and review the potential benefits, limitations, and risks before testing.[3] Furthermore, a patient's preferences regarding the receipt of germline information, including the choice of declining it, should be carefully ascertained.

In practice, a report of IFs/SFs may include complex considerations, including results returned to whom, how much information to disclose, results returned by whom, and what actions (i.e., follow-up testing and/or care) will take place after disclosure of results [39]. For instance, a disclosure framework as a flowchart in the context of clinical treatment was suggested, which would enable physicians and patients to discuss preferences for receiving IFs/SFs and follow-up options (see p. 290 in [39]).

17.1.4 Secondary Germline Findings in Genomic Tumor Profiling and Public Attitudes

As explained in the previous section, cancer patients undergoing genomic tumor profiling have to make decisions on whether or not to learn about germline SFs and when, to whom, and how to convey the information to their family members, along with decision-making on their own treatment options. This leads to the question of what the attitude is of the cancer patient toward germline findings in such testing. Some qualitative studies have reported that advanced cancer patients were highly interested in learning about secondary germline findings, and they perceived both various benefits and concerns regarding the limitations in clinical utility and the emotional burden or distress derived from such information [40, 41].

[3] The ASCO *Policy Statement* also suggests that oncologists should discuss the possibility of detection of high-penetrance variants among their patients, which has not been suggested by personal and/or family history; less well-understood or lesser-penetrance variants; and variants of uncertain significance (VUS) in multigene (multiplex) panel testing.

We would like to share data obtained from a survey in Japan, where genomic tumor profiling tests to identify tumor-specific genomic changes and find molecular-targeted drugs among patients with advanced cancer have been covered by the national health insurance scheme since June 2019. Some of the tests can identify germline variants including *BRCA* or *TP53*, which are putative candidates owing to their actionable natures, per the recommendations of the ACMG [29, 31]. A cross-sectional survey including Japanese cancer patients, family members of cancer patients, and general adults in 2018 revealed that family members and cancer patients highly evaluated the potential benefits of tumor profiling tests. This was expected to facilitate diagnoses and treatment of patients and their family members, and the detection of any heritable oncogene would facilitate the development of future plans [42]. On the contrary, approximately 20% of respondents in each group did not wish to know whether they had a hereditary disease, and >30% of them worried about the possibility of being discriminated against owing to their genetic condition. However, irrespective of the results, the family members were more willing to share information regarding germline findings than the patients. Owing to concerns regarding anxiety and stress among family members, 3.8% of cancer patients preferred not to share this information. Only 1.8% of family members agreed with this notion, with the most common reason being "It is better for me not to know."

Informed consent forms for the tests provide alternatives for patients regarding whether or not they want to know the test results, including the possibility of hereditary cancers as SFs, and whether or not they would be willing to share this information with their family members. Furthermore, a column is available to provide the names and contact information of the family members, in case the patient is unable to share information with the family members for any reason, including changes in physical conditions.

Since patients tended to overestimate the benefits of tumor profiling for personalized treatments and potentially ended up disappointed, information and decision aids (DAs) are needed to support medical professionals in communicating the realistic benefits and risks associated with the results [43].

17.1.5 Data Sharing and Privacy Issues in Genomic Research and Public Attitudes

The previous sections primarily focused on genomic analysis in the clinical setting; however, here, we discuss this in the context of basic research. Sharing of clinical and genomic data among researchers has been a standard practice in genomic research. Some platforms for global sharing of clinical and genomic data have been developed, such as the Global Alliance for Genomics and Health (GA4GH), where more than 600 organizations and companies from more than 90 countries participate [44]. BRCA Exchange aims to advance understanding of the genetic basis of breast, ovarian, pancreatic, and other cancers by pooling data on *BRCA1/2* variants and corresponding clinical data worldwide [45].

Data operators may adopt an approach such as collecting data in a temporarily closed location within the database for the same disease and releasing it after findings from several studies have accumulated. Institutional review boards (IRBs) also play important roles, and they should require researchers to show their data-sharing plan and check whether the data have been submitted to a database as planned. Furthermore, since social and public understanding is indispensable, ideas are needed to get research participants and the public interested in how genomic and clinical data are used and shared in genetic research. In the USA, the National Institutes of Health (NIH) issued Genomic Data Sharing Policy (GDS Policy) in 2014, which defined responsibilities of investigators, data submission expectations, as well as conditions for research use of controlled-access data (available for users meeting specific requirements, including an approval from a data-access committee) and unrestricted-access data. The data submitter needs to take measures to lower the risk of reidentification by not adding identifiable information to a database initially. The idea of the GDS Policy has been adopted by data repositories in other countries.

In genomic studies on cancer and rare diseases, not only patients but also their family members may provide valuable information. Therefore, protocols to protect both patients and their family members are needed in such studies and on data-sharing platforms. This leads to the question of the concerns regarding sharing data including those of family members. For instance, since cumulative data from both patients and their family members are valuable for genomic analysis, some participants may feel implicit or explicit pressure from researchers or other family members. Although the participant's right to withdraw consent is crucial, withdrawal from the study by certain family members may be difficult when data and samples are already shared internationally. There is risk of identifiability not only for identifying the individual who provided the data but also for his/her family members, especially when family trees are published in the article. In such situations, existing data-sharing policies may not be enough to protect family members.

As data sharing has become increasingly important, confidentiality and privacy issues involved therein have also gained increasing importance. A questionnaire survey in Japan indicated that public (especially patients, compared to healthy adults) concerns were higher with respect to the sharing of their own data with those of their family members, and they expected stronger protection mechanisms, compared with only their own data being shared [46]. A systematic review revealed that research participants and the public attitudes toward genomic data sharing were influenced by various factors, such as their perceptions of sensitivity and controllability of genomic data, perception of potential risk and benefit of genomic data sharing, sensitivity and controllability of genomic data, and governance-level considerations [47]. Global empirical studies showed that general public were most likely to donate their genomic and health data for clinical and research use, but unwilling to donate them to for-profit researchers or company researchers, compared to medical doctors and nonprofit researchers [48, 49]. In a study in the UK,

the public raised concerns about managing flows of information to protect patient confidentiality and guard against unauthorized access to data by third parties, such as employers, marketing companies, and insurers [50].

Cloud computing, a model whereby users rent computers and storage from large data centers, has been expected to promote large-scale collaboration in cancer genomic medicine. We need to argue the challenges of managing genomic data in the cloud and be ready to inform patient and family about data safety and privacy [51, 52].

17.2 Clinical Ethics in the Diagnosis and Treatment of Hereditary and Other Cancers

We further discuss ethical perspectives in the clinical setting with respect to the diagnosis and treatment of HBOC and other hereditary cancers.

17.2.1 Clinical Ethics in Cancer Treatment: Perspective Based on Quality of Life

In making decisions during cancer treatment, careful assessment and improvement of the quality of life (QOL) of the patients are highly significant. Clinical ethics in cancer and oncology nursing have further emphasized the impact of cancer and cancer care on sexuality, sexual behavior, and fertility and on changes in body image resulting from the dissection of organs including the breasts and ovaries [53]. Therefore, the SDM approach is effective here again for patients and medical professionals to predict long-term outcomes of surgery or pharmacotherapy.

In SDM, clinicians and patients are encouraged to use various decision aids (DAs), such as leaflets, video clips, and websites. DAs are not intended to encourage a patient to select or consent to a particular course of action, but rather to support patients and clinicians in identifying and implementing the healthcare options most aligned with the patient's individual preferences and values [54]. The Ottawa Personal Decision Guide (OPDG) was developed as a tool to be used in healthcare [55]. A decision-maker fills out the OPDG form to organize his/her opinions regarding specific treatment options or testing and their merits and demerits, along with his/her knowledge and values, the availability of support, and certainty. The form may be used to promote discussion between the decision-maker and the clinician supporting the decision-making process. Furthermore, DAs have been developed for specific diseases (e.g., a DA is available for decision-making regarding surgery for breast cancer patients).

It is important that the discussion process itself is the means, not the end, for the patient to make a confident decision. The SDM approach may predict patient expectations and concerns, along with long-term effects, not only regarding medical outcomes but also life, work, and QOL.

17.2.2 Prophylactic Surgery: Decision-Making and Follow-Up

Based on the SDM approach and the perspective of QOL, the specific care required for patients with HBOC with a genetic predisposition to breast and ovarian cancer can be evaluated. This information would potentially support decision-making regarding prophylactic surgery and postoperative follow-up among patients. Risk-reducing mastectomy (RRM) and risk-reducing salpingo-oophorectomy (RRSO) are cost-effective preventive strategies in *BRCA1/2* mutation carriers [56]. While prophylactic surgery is an effective lifesaving measure and helps alleviate the fear of developing cancer among women, it may also have a great impact on their QOL and self-image. A systematic review reported that women's decision-making regarding RRSO was affected by demographic, clinical, and psychological factors, as well as family history of cancer, rather than an objective cancer risk [57]. Another systematic review reported that most studies assessing psychosocial aspects reported high levels of satisfaction among women deciding to undergo RRM; however, greater variation was observed in satisfaction levels from a cosmetic perspective, and satisfaction with body image was diminished along with sexual feelings, especially after bilateral risk-reducing mastectomy (BRRM) [58]. An interview-based study in Canada reported that nearly one-half of the women who underwent RRSO did not believe that they were well-informed about postoperative outcomes including anesthetic effects, physical symptoms, menopause symptoms, or return to daily activities, despite fully receiving pre-surgery counseling [59]. Deliberated assessment and support in decision-making before surgery and during postoperative follow-up are required.

According to the HBOC registration system in Japan, only a few *BRCA1/2* carriers have undergone RRM and RRSO in Japan, compared to their European and American counterparts [60]. The guidelines of the Japanese Breast Cancer Society (2018) and Japanese Society of Gynecologic Oncology (2020) recommend that prophylactic surgery for women carrying *BRCA* variants who have not developed cancer, which is not covered by public health insurance (as of 2020), is desirable for the approval of the clinical ethics committee at each institution, although no such requirements are specified in the National Comprehensive Cancer Network (NCCN) guidelines. In clinical conferences, medical professionals have to assess the "beneficence" and "non-maleficence" for prophylactic surgery in each case. In addition, in terms of respect for autonomy, they have to provide a patient with complete explanations of both the benefits and risks of prophylactic surgery and respect the patient's autonomous decision.

17.2.3 What Method May Be Useful in the Clinical Setting? Four-Quadrant Approach of Clinical Ethics

In clinical conference or case studies, the four-quadrant approach for clinical ethics, which was originally introduced by Jonsen et al. (1992) [61], may be a useful approach to better understand the complexities and ethical dilemmas of a case. The method comprises four aspects, medial indication, patient preference, QOL, and

Table 17.2 The four-quadrant approach of clinical ethics: checkpoints for prophylactic surgery

Medical indication	Patient preference
What evidence and data are available worldwide?	Does the patient have a capacity for decision-making or expressing will?
What is the best timing for the patient?	Does the patient fully understand the positive outcomes of *BRCA* variants and RRM or RRSO? Do they have a strong desire and motivation to undergo surgery?
What are the benefits and risks/disadvantages of the surgery?	What is the patient's sexual orientation and gender identity (SOGI)?
Is there a provision for physical/psychosocial care after surgery?	Does the patient intend to become pregnant?
Are follow-up options (surveillance, cost, and medical institution) available for both patients who undergo the surgery and those who do not opt for surgery?	Has the patient been informed of the effects of surgery on sexual activity and gender identity, and how much do they value them?
QOL	**Contextual features**
Subjective QOL: What is the status of the breast and ovarian cancer among the patients?	What intentions do the patient's family or stakeholders have? How do they evaluate the surgery?
What do patients wish to deal with regarding the illness, and how do they want to live their lives?	What are the institution's and medical team's policies? What is the system for research and education?
Objective QOL: What scale and measures should be used to evaluate?	What are the financial aspects of surgery and postsurgical care? Are costs incurred by the patients themselves or public medical services?
By whom should QOL be evaluated and what criteria should it be based on?	What are the religious beliefs and cultural customs, and is there a potential influence on other patients and society?
How would the QOL of the patients change with time and as a consequence of medical intervention?	What are the other factors or concerns (e.g., timing, social background, and communication strategy with the patient's genetic relatives)?

contextual features; several inquiry-based checkpoints are provided for each topic. Muto and Takashima (2017) [62] suggested adapting this approach in considering ethical issues associated with prophylactic surgery. Table 17.2 summarizes illustrative checkpoints for prophylactic surgery.

Regarding "medical indication," medical conditions including diagnosis, prognosis, the aims of intervention and care, and the balance of risk and benefit should be considered. To respect "patient preference," it is important to understand what explanations have been provided to the patients and their understanding of them. It would be helpful for physicians to check casual remarks and questions from the patient. QOL encompasses various components including physical, psychological, social, and spiritual. "Objective QOL" may be measured using certain scales, whereas "subjective QOL" may be better understood through mutual communication with patients. Furthermore, "contextual features," such as family members or other stakeholders, financial aspects,

institutional policies, and any other points potentially influencing decisions, should be considered. From the point of diversity, patients' views of cancer or preferences toward prevention strategies may depend on cultural background, ethnicity, socioeconomic status, religious belief, and generation [63]. This method would help medical professionals collect information and understand the types of conflicts occurring in different cases.

17.2.4 Patient Confidentiality and Disclosure of Genetic Information to At-Risk Relatives

Another challenging controversial debate concerns patient confidentiality and the disclosure of genetic information to their at-risk relatives, since genetic information is partially shared among the genetic relatives of patients. Medical professionals are required to maintain the confidentiality of their patients or clients, and they may face dilemmas of whether they have a duty or are permitted to disclose genetic information with the patient's relatives, especially when patients do not provide consent. Laws and principles vary among different countries, and several lawsuits have emerged regarding this issue.

In the USA, two lawsuits in the mid-1990s yielded different judgments. In the *Pate* v. *Threlkel* case in Florida (1995), the court concluded that a physician's "duty to warn" a patient's (medullary thyroid carcinoma) relatives could be satisfied by simply notifying the patient. However, in the *Safer v. Pack* case in New Jersey (1996), the court held that a physician had a duty to warn those known to be at risk of avoidable harm from a genetically transmissible condition (multiple polyposis) [64]. However, since the Health Insurance Portability and Accountability Act (HIPAA) of 1996 Privacy Rule came into effect in 2003, healthcare providers are neither required nor permitted to warn relatives without the consent of their patients [65]. ASCO updated policy statements (2003; 2015), which indicated that oncologists should explain the importance of sharing test results with at-risk relatives, such that they may benefit from this information during the obtainment of informed consent and pretest education [38]. Similarly, the American Medical Association (AMA) *Code of Medical Ethics* states that physicians should discuss with the patient the medical and psychological implications for the individual's biological relatives, and they will be available to assist in communication with the patient's relatives (Opinion 4.1.1) [66].

A recent case, *ABC v. St George's Healthcare NHS Trust & Ors* (2020), was the first lawsuit that argued patient confidentiality and the duty of medical professionals to disclose genetic information to genetic relatives in the UK [67–69]. Although the High Court concluded that the claimant *ABC* (a daughter of a male patient diagnosed with Huntington's disease) lost the case, it also added that it was reasonable to impose a duty on the medical teams to balance the daughter's interest in being informed of her genetic risk against her father's interest in preserving confidentiality in relation to his diagnosis and the public interest in generally maintaining

medical confidentiality [69]. This duty does not require physicians to directly disclose genetic information to the daughter, nor are the medical professionals generally responsible for the genetic relatives, but rather this duty encourages them to carefully balance the interests of family members.

In Europe, laws and principles are different, i.e., in France, a bioethics law revised in 2011 requires the patient provide information regarding the diagnosis of a pathogenic variant associated with a serious disease that is preventable or treatable among at-risk relatives. This is to be done either directly or by providing consent to healthcare professionals to contact relatives (although in practice, patient disclosure is preferred and it is rare that physicians directly disclose information to the relatives) [70, 71].

In Australia, although state laws differ, healthcare professionals have no legal duty to inform genetic relatives. However, disclosure is allowed under the *Federal Privacy Act 1988* as an exception if there is "reasonable belief that disclosure is necessary to lesson or prevent a serious threat to life, health or safety of a genetic relative" (i.e., disclosing the sister of a woman receiving a positive test result on *BRCA* variant analysis) [72]. This exception was further corroborated by a National Health and Medical Research Council (NHMRC) guideline (2014), which provides a framework and specific steps for healthcare professionals to use or to disclose genetic information (i.e., advise patients to contact relatives, appropriate expertise to assess whether the threat to genetic relatives is serious and disclose as necessary) [73]. Such a practical framework in exercising discretion may also help healthcare professionals to better balance patient confidentiality and benefits of at-risk relatives.

In summary, there is no conclusive evidence regarding the worldwide unconditional invalidity of patient confidentiality. Disclosure to at-risk relatives without patient approval is limited to particular situations, e.g., when a genetic variant is associated with serious and actionable health conditions. In the practical context, patients or index persons may usually take on the primary role of communication among their family members.

17.2.5 Communication of Genetic Risk Within the Family

From the perspective of genetic relatives, being informed about an increased risk of hereditary cancer may be useful for early cancer detection, the choice of whether "to know or not to know" their genetic information, risk management, and future life planning. However, patients or index persons in the family usually face difficulties in communicating with their genetic relatives, which may also lead to conflict among them.

Numerous empirical qualitative and quantitative studies have revealed dilemmas and practices for familial communication about HBOC. Several studies indicated that *BRCA* carriers (both patients and asymptomatic carriers) or at-risk persons often feel responsible for communicating with their genetic relatives [74, 75];

Table 17.3 Factors associated with the teller's view and experience

Categories	Examples
Value and norm	It is beneficial to know everything, ignorance is bliss, openness in the family, the importance of a relationship based on trust, responsibility or the sense of a mission to share information
Knowledge and experience	Medical and genetic literacy, experience with health and illness, educational background, occupation
Health and psychological conditions	Current physical and mental health, disease course, perception of the family history and one's own genetic risk
Benefit/concern	Feeling relieved in keeping the information concealed, sharing one's feelings and worries, providing or gaining support from family members Psychological burden of communication, difficulties in the timing of communication, possibility of receiving a negative response

however, their decision-making of whether to tell, whom to tell, and what and how to tell depends on the case and is dependent on various factors. Situations are different in communicating with offspring (especially young children and adolescents) and with other genetic relatives including siblings, cousins, and parents. Patients may decline to have such communication with their family members in an effort to protect their relatives (e.g., from painful knowledge or potential discrimination), due to difficulties in overcoming preexisting conflicts or rifts within the family or due to feeling that certain relatives did not "need" to be provided such information (e.g., believing that boys and other male relatives do not need to be provided such information) [76]. Studies have reported that sex is an influential factor, since numerous patients speculated that the risk of cancer associated with *BRCA1/2* variants was higher among women than among men [77]. Furthermore, physical/emotional distance (i.e., having no contact) with the relatives matters. Quantitative analysis revealed that the information dissemination rate depended on the type of relative; information dissemination rates were the highest among siblings, followed by parents and children (first-degree relatives), aunts/uncles, nieces/nephews (second-degree relatives), and lowest among cousins (third-degree relatives) [78, 79].

Regarding parent-children relationships, the age of the children, maturity, cognition, personality, and emotional readiness influenced parental decision-making, and sometimes parents decided that it was not the right time to tell their children at least at that point [80].

Based on previous studies of hereditary diseases including those associated with *BRCA* variants and our studies in Japan, we found various factors associated with decision-making related to communication within the family. Views and experiences of the teller (individuals who attempt to share information with their family member, either the patient having undergone genetic testing, at-risk individuals, or sometimes their partners) matter (Table 17.3), as well as the teller's presumption with the listener (e.g., children, siblings, parents, cousins, and aunt/uncle) (Table 17.4).

Table 17.4 Factors associated with the listener presumed by the teller

Categories	Examples
Knowledge and experience	Medical and genetic literacy, experience with health and illness, educational background, occupation
Attribute	Sex/gender, age
Receptivity	Comprehension, readiness, life condition
Relationships	Physical distance (living together or separately), psychological distance (intimacy)
Benefit/concern	Early disease detection, changing/improving lifestyle habits, choice of preventive or therapeutic measures, the opportunity to participate in clinical trials, the choice of presymptomatic or diagnostic genetic testing Psychological burdens, negative impact on life decisions including marriage and childbirth

Therefore, difficulties in and the optimal timing for communication with family members may differ in a case-specific manner. Medical professionals may not only directly contact relatives or encourage clients to share information with their relatives, but they may also assist clients in communicating their relatives and provide psychoeducational guidance or written information aids. Genetic counselors could introduce the topic and discuss the pros and cons of communicating them with children [80]. Furthermore, local programs and books and videos serve as supportive resources for children to learn about cancer [77, 78].

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