Case Report

To use or not to use? an ethical analysis of access to data and samples of a deceased patient for genetic diagnostic and research purposes

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Abstract:

Using genetic tests on deceased patients' samples for diagnostic purposes affects the family members' health and lives but raises some ethical issues in today's practice of medicine and research. In this paper, we address a common ethical dilemma of clinicians regarding whether to perform genetic tests on a deceased patient's sample upon a request from first-degree relatives against the patient's wishes in the last days of life.

In this paper, a real case scenario is presented that echoes the above-mentioned ethical challenge. Reviewing the genetic basis of the case, the ethical arguments for and against the reuse of genetic material in a clinical context are discussed. An ethico-legal analysis of the case is proposed based on Islamic medical ethics resources. As reusing stored samples of expired patients without their consent also challenges the researchers in the field of genetics, a debate is included on the post-mortem use of genetic data and samples for research.

Finally, defining the special features of the presented case and positive benefit-risk ratio, it is concluded that reusing the patient's sample may be justified if the first-degree family members insist on genetic testing and are comprehensively informed about the benefits and harms.

Keywords: *Genetic information; Postmortem disclosure; Ethics; Family members; Confidentiality; Consent.*

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Introduction

Genetic technologies help improve health and prevent diseases. Monogenic diseases can be identified by genetic testing, and genomic testing detects illness risk factors, including several genes (1). Therefore, these technologies can discover traits in a patient's DNA that may affect her/his health, aiding doctors in preventing or delaying the onset of ensuing illnesses, estimating disease risk for family members, and avoiding transmitting these hazards to descendants (1).

The development of diagnostic genetic technologies has been associated with novel ethical issues (2,3). Genetic technologies involve the handling of highly personal information that could have far-reaching consequences for patients and family members (1). Using a genetic test in an asymptomatic person to predict the future disease risk has significant effects on the family members' health and lives but can lead to inevitable family conflicts (2,3); hence, it is essential that it be practiced with due regard for ethical, legal, and societal factors (1). Communicating about a familial genetic risk outside of the context of a patient-doctor relationship is a contentious ethical and legal problem that has been debated for years (4).

Biotechnological applications also challenge Western individualism (2,3). Implementing the principle of respect for autonomy can create ethical difficulties and controversies that convey a Foucauldian doubt about the indisputable truth of autonomy (2). Although new genetic technologies are more affordable and faster, the simple act of reviewing family information still forms a significant part of the daily routine of genetic evaluation. Genetic testing of a relative is sometimes necessary for accurate genetic testing on the person seeking advice (5). In some cases, patients requesting genetic counselling should have access to information about their relatives' conditions and genetic traits. If a family member is dead and has not specified how his/her medical records can be used posthumously, obtaining his/her consent is not feasible (5). Hence, it is reasonable to expect at-risk family members to be interested in receiving the genetic results of deceased relatives, which may impact their health (6).

Nevertheless, whether to disclose the genetic information of a deceased patient to family members is a controversial issue needing ethical analysis (6). There is an agreement that genetic

data, such as clinically significant and actionable genetic abnormalities, should be shared with patients. However, there are fewer agreements on how best to share hereditary risk information with family members from a genetic perspective (6). A similar approach has been adopted in the Iranian medical context. Article 89 of the Iranian Code of Ethics for Medical Professionals conveys that re-using a patient's genetic information and samples is permitted only by the patient's consent or for anonymous use (7).

In what instances, if any, do physicians have an ethical obligation to share this genetic risk knowledge with relevant family members, or can they re-use the patients' samples for family members' genetic tests? It is one of the most important unresolved questions (4). Following a patient's death, when consent cannot be legally obtained, the issue of whether or not to disclose genetic information to family members becomes very prominent (6). In cancer cases, the patients' relatives may benefit from risk assessment and more precise treatments through genetic and genomic testing, and ethical issues are more significant (8).

Whether using and sharing identifiable research data after death is ethically permissible is questionable. Therefore, in this article, access to data and samples of a deceased patient for genetic diagnostic and research purposes is ethically analyzed. To achieve this goal, a real scenario is presented and the arguments for and against using genetic data against the patient's consent are put forward in an effort to answer two pivotal questions: Is it ethical to use the deceased patient's data samples for diagnostic purposes for relatives? Is it ethical to use the deceased patient's data and samples for research purposes?

Real Scenario

A 59-year-old man with primary myelofibrosis (PMF) was treated with hydroxyurea for five years. He was referred to the hematology department for fever, pneumonia, and pancytopenia. Bone marrow biopsy showed hyperplasia and fibrosis. The patient reported a positive family history of cancer in first-degree relatives (his father had laryngeal cancer and his sister had a brain tumor) and second-degree relatives (his cousin had a brain tumor). He was a candidate for bone marrow transplantation. An eligible donor was not found, and chemotherapy was ineffective. Unfortunately, he died a few months after confirmation of the blast phase. Tumor genetic tests were performed to find targeted therapies for the patient based on the detected mutations. Because of technical issues, the results of genetic tests were prepared a few months

after the patient passed away. The family genetic consulting was performed to propose additional genetic tests to the first-degree family members that included only two members: the patient's sister and daughter; however, targeted genes for this disease have no X-linked inheritance. Although the patient had verbally refused to re-use his blood sample for relatives' genetic tests in the last days of his life, the family members insisted on further genetic evaluation of the patient's sample. However, the patient's refusal was not obtained through a valid written informed process, and he also did not mention his decision regarding re-using the sample after his death.

Discussion

Genetic basis of primary myelofibrosis

Primary myelofibrosis (PMF) as a myeloproliferative neoplasm is defined by widespread fibrous tissue in the bone marrow and an increased number of myeloid cells. It is accompanied by extramedullary hematopoiesis, organomegaly, pancytopenia, and an altered cytokine expression profile (9). One-third of the patients (30%) have no symptoms and are detected inadvertently, usually due to an abnormal blood count or splenomegaly (10). In the asymptomatic phase, it is difficult to identify and diagnose most PMF cases. The patients may remain symptom-free for many years (9, 11).

Severe anemia, marked hepatosplenomegaly, fatigue, night sweats, fever, cachexia, bone pain, splenic infarction, pruritus, thrombosis, and bleeding are the clinical manifestations of PMF (12). The cause of death associated is frequently attributed to heart failure, infection, hemorrhage, or acute leukemia (approximately 20% of PMF patients) (9). In asymptomatic patients, clinicians may consider delaying treatment until symptoms appear. This approach is known as "watch and wait" (11). In symptomatic patients, a number of new medications are under ongoing trials. However, allogeneic stem cell transplantation is the only established treatment for PMF in very high-risk patients based on mutations and karyotype. It is a highly experimental procedure; therefore, it is difficult to achieve a cure (9,12).

A critical issue is the patient's survival, which is 3.5 to 5.5 years from diagnosis of the disease. In familial cases, the 10-year survival rate is only 30% (9). Compared to more distant relatives, the first-degree relatives of the patients have a 5-7 times elevated risk (9). A dynamic model of the International Prognostic Scoring System (IPSS) (DIPSS) was used to estimate a patient's survival

(13). Recently, GIPSS (genetically-inspired prognostic scoring system) and MIPSS70+version2.0 (MIPSSv2; mutation and karyotype enhanced international prognostic scoring system) have been presented for survival assessment (12). Previous studies showed a worse survival in PMF associated with nullizygosity for the special haplotypes of JAK2 and in patients with a low JAK2 allele burden (13). Therefore, the identification of JAK2 somatic mutation is valuable in estimating the survival.

The presence of mutations in JAK2, CALR, or MPL is anticipated in approximately 90% of the patients. These mutations are also prevalent in other myeloproliferative neoplasms, including polycythemia vera (PV) and essential thrombocythemia (ET). In the presence of a positive family history, these mutations support the probability of PMF (12). In new prognostic models, the mutations and karyotypes are pivotal in assessing the patient's survival.

The bioinformatic analysis of this patient's exome sequencing data revealed several genetic variants in important cancer genes, including *JAK2*, *IDH1*, and *CHEK2*. The somatic variants in the *JAK2* and *IDH1* may be important for targeted cancer therapy to overcome resistance in this patient. The variant in CHEK2, known as the germline cancer predisposition variant, may be related to familial cancer in the patient's pedigree (PMID:19401704). Therefore, genetic testing in asymptomatic family members may help to detect high-risk individuals.

Ethical arguments for disclosure and re-use of genetic material

Beneficence principle: A dynamic approach to medical intervention based on genomic risk information is accessible. Blood relatives can learn about their genetic risk through family genetic testing and act proactively (8). It is predictable that conditions that are unpreventable or untreatable at present may become manageable in the future (14). It is argued that disclosure is beneficial, mainly if the hereditary condition is treatable or preventable (6). For specified mutations like BRCA1/2, relatives might consider prophylactic surgery to prevent advanced cancer if they are aware of a specific mutation. Furthermore, a genetic test result can be psychologically beneficial, especially if it helps to better understand the cause of a familial disease. (6).

Genetic information may benefit relatives, assist in reproductive decisions, and influence their future lives. Furthermore, knowledge of the genetic makeup could provide them with meaning.

Sharing information with family members enriches well-being by enabling them to take control over their lives to some extent (6,15). The relatives' genetic

right to know is fundamentally based on autonomy and control (15). Whether physicians have a duty to improve the family members' autonomy remains controversial. Physicians are not obligated to improve the welfare of the patients' families at all times since it may interfere with their primary duties. Is it reasonable for a physician to support the autonomy of a family member without a physician-patient relationship? (6,15) In recent decades, the emphasis on the self-determination and well-being of patients has formed the concept of autonomy. However, there has been uncertainty about the family's involvement in a competent patient's medical decision-making, which is supported by the recently proposed notion of "*relational autonomy*" (16). Relational autonomy, originally a feminist concept, regards "*individuals' identities, interests, ends, and beliefs as fundamentally dynamic, continually constructed and reconstructed in dialogic processes with other people*" (17). Relational autonomy is a meaningful substitute for autonomy in clinical genetics, as it addresses genetic information that is, by its nature, shared and related to the patient's family members (18). Conceptually, pursuing informed consent based on individualistic autonomy increases the inherent complexity of real genetic cases. Treating the patient's consent as a person's decision hinders shared decision making in the family members from whose wellbeing and self-determination are affected by the individual patient's choices (18).

Concept of shared possession of genome: Despite the DNA commonalities in humans, each person has a unique genome arrangement. It is not uncommon for first-degree relatives to receive a significant percentage of this package (6). Genetics was developed by family linkage studies illustrating an individual's genetic risk. Moreover, according to some scientists, genetics is a form of family inheritance (2). Additionally, a specific medical diagnosis can profoundly impact close relatives' health, and test results could even cause harm to relatives (6). Gordon et al. found that participants believed genetic information was shared property. They believed that genetic information should be shared rather than controlled and that the concept of autonomy on personal information was not applicable (15).

Accordingly, regarding the idea of shared possession of DNA with biological relatives, there is an argument that biological relatives should have access to the patient's genetic information to

determine their risk of genetic diseases (6). There are some arguments in medical sociology and anthropology about the concept of kinship and new forms of responsibility to offspring and next-of-kin based on genetic material (19). The degree of relatedness and the concept of next of kin is an essential issue in this idea, and these terms should be recognized in countries' legal systems (5,6). Some commentators have suggested the necessity of kinship ethics, which derives from conflicts of interest caused by sharing genetic material and data between relatives (20,21).

Regarding kinship ethics, moral creatures should avoid interfering with other creatures' survival efforts (22). However, by considering DNA as shared property, people may be restricted in their autonomy. Therefore, the shared property concept is debatable (6), and the individualist perspective of ethical issues raised by genomic data could be controversial (2).

Duty to warn relatives and right to know: There is an argument that physicians should inform a patient's relatives about the gene-transmitted disease when certain conditions apply. The information should be informed to relatives if it includes a condition that may result in severe, impendent, or undeniable harm, and there is treatment or prevention. Early diagnosis is often associated with the early treatment of certain conditions, while late detection often results in an incurable condition (6). Physicians generally encourage patients to tell their relatives about genetic risks during their lifetime. It is no longer possible after their death, making a clinician's duty to care more critical, especially if genomic data become available only after their death. However, because of the patients' confidentiality and privacy issues, the duty of physicians to notify family members is not unlimited. (6). Gordon et al. found that contrary to presumed values of the patients' privacy, the participants (patients and their relatives) agreed to share information even after death (15).

In the case of ABC v St George's Healthcare NHS Trust, an English man with Huntington's disease was unwilling to disclose the diagnosis to his pregnant daughter because of concerns about her decisions about abortion (4). The Court of Appeal concluded that, depending on a particular case, a clinician's obligation to warn a patient's relatives of increased genetic risk could be fair and reasonable (4). The court also suggested that if relatives would gain nothing with information disclosure (because of no available preclinical diagnostic tests, approved treatment, or after childbearing age), physicians have no duty to warn and care for them

(4). Hence, genetic health policy should focus on culture and reproductive choice in decision-making about the disclosure of genetic data (22).

Another issue is that a legal duty to warn should be extended to whom as a genetically at-risk relative (14). It is necessary to define the term “family members” (to whom genetic data should be disclosed). This definition must be under the laws of each country; for instance, in the United States, "family member" means anyone from the first to the fourth-degree relative as defined by the Genetic Information Nondiscrimination Act of 1988 (14).

Due to direct-to-consumer technology, healthcare providers are no longer involved in the initial steps of genomic sequencing. Nevertheless, they have an essential role in counseling patients and at-risk relatives. Moreover, a pivotal matter is that the warning should be delivered appropriately understandably regardless of the person that provides it (a patient or a healthcare provider) (14). However, the patient should be warned that if more genetic information is available, it is linked to a wide range of other data, and new clinical implications are continually being discovered (14).

Ethical arguments against disclosure and re-use of genetic material

Nonmaleficence principle: Physicians have an obligation not to harm patients. The same can be asserted about their moral duty to inform family members about genetic information. Family members may suffer emotional and socio-economic damage if such information disclosed. The harmful effects of this approach have been suggested numerous times, but the empirical evidence that supports them is minimal. On the contrary, some believe that if the disclosure is denied, the right to know could be violated because it could be paternalistic. (6).

Genetic information and counseling processes also play an essential role in determining psychological harm. Keeping the information secret can also have adverse effects if the results are relevant for preventing or treating relatives. Additionally, unconsented disclosure of confidential information may cause harm to the deceased patient and may have possible implications for the family (6).

The right to privacy: Privacy is the individual's right to limit access to his/her personal information. Although four categories of informational, physical, decisional, and proprietary are proposed for the concept of privacy, it is associated with some ambiguities, especially in the field of genetics (23). Within the physician-patient relationship, confidentiality, which is rooted in informational privacy, prohibits the disclosure of medical information to third parties. Despite being a

fundamental part of current and ancient doctors' medical oaths, it can be disregarded in certain circumstances, such as the safety and health of third parties (23). Most ethical frameworks, including the World Medical Association and the General Medical Council, extend confidentiality beyond death to protect patient privacy (5). However, the notion of genetic privacy is controversial. Genetic data are a unique identifier for owners, but it can have significant implications for family members and relatives' health (23). People assume that genetic information is more private than other personal information and believe that such data is specific to them. This perception is called genetic exceptionalism (23).

Contrary to the dominant perspective, Breitkopf et al. found (8) that fewer than 10% of the participants in a pancreatic cancer biobank based at Mayo Clinic in Rochester agreed with the non-disclosure of information with relatives if it would be of medical benefit. The concern for privacy within the family after death was even lower (8). The GMC considers some conditions regarding requests for deceased patients' information, including the probability of causing distress or benefit to the patient's partner or family, the possibility of anonymity, and the purpose of the disclosure. When balancing the considerations, the deceased patient's wishes should be considered (5).

The right not to know: Some studies revealed that some people are not interested in their genetic status. According to one study, 50–75% of the family members of patients with BRCA mutations were willing to participate in a mutation screening program (6). Another study found that blood relatives of pancreatic cancer patients agreed with sharing the patients' genetic information with them. This is in contrast with the common belief that information sharing causes feelings of stigmatization and vulnerability in relatives (8). This information may be shared against the preference of the relatives not to be informed, which compromises their autonomy. The unrequested disclosure of genetic information may violate family members' autonomy even if they are unaware that genetic information is available and will diminish autonomous decision-making. Although unrequested disclosure of genetic information could breach the right to privacy, depending on other concerns, including whether disclosure may benefit a relative, a balance should be considered between their interest in not knowing and their desire to know (6,8,4).

Deceased person's wishes (respect for autonomy):

Autonomy conveys an independent agent's self-governance and making decisions between alternative choices (24). Family members are morally expected to fulfil the wishes of the deceased, so the explicitly declared unwillingness of a dead patient to disclose his/her certain information should be taken into account (5). The General Medical Council has emphasized that disclosure or non-disclosure of information after a patient's death depends on the patient's explicit desire. Therefore, healthcare professionals should comply if the deceased patient has requested that their data be kept private (25).

As a patient's autonomy depends on capacity and competence, it is problematic to consider his/her autonomy after death. According to some researchers, the deceased's patient autonomy should be respected by a physician because if those wishes are not honored after death, then the physician violates the patient's autonomy, and the concept of autonomy is diminished. Moreover, it could affect public trust in healthcare professionals (6). On the contrary, it may conflict with the relatives' interests. The health-related interests of the family members could be considered in the risk-benefit of breaching the deceased patient's wishes. Furthermore, it is complicated to find out what the deceased patient's true wishes were in many cases (6). Breitkopf et al. found that most participants believed that if the information benefited relatives, the family benefit should be preferred over individual wishes (8).

An Islamic ethico-legal approach

The Islamic legal and ethical maxim pertinent to this case is the principle "*No Harm, No Harassment*." The principle is derived from the prophet hadith "*la darar wa la dirar*," which refutes acts of deliberately harming oneself and others (26). This principle has its source in both revelation and reason and is famous among Sunni and Shi 'a scholars (27). Darar is translated into "*harm*" and means "*detriment, loss*," the opposite of "*benefit*," and conveys any detriment or loss suffered by a person to himself, his property, dignity, or personal interest. The second term is dirar that was translated as "*harassment*" by Sachedina and means "*harming, injuring, or hurting in return*." both harm and harassment are determined by custom(al-'urf) (27). Islamic ethics methodology includes a careful analysis of harm and benefits while demanding that obligations of preventing harm be prioritized over promoting good (27). Hence, we must prevent harm to the patients and their family members. Depriving family members of genetic testing causes them essential physical and psychological health issues.

Re-using the deceased patient's blood sample against his/her preferences violates the patient's right to "*Izn*". The Islamic legal maxim translated into permission and conveying the meaning of the English word of consent.

Nevertheless, the question is whether the patient's right to permission (izn) remains after death according to Islamic law? To answer this question, one can argue that in Islamic jurisprudence, one of the pillars of the validity of permission (izn) is the capacity of the person who gives permission (28). Article 956 of the Civil Code of Iran, based on Islamic jurisprudence, states that the capacity to possess rights ends with death. Therefore, it can be concluded that the patient's right to give permission ends with death (29). A similar approach is taken in Islamic countries regarding the individual's permission for organ donation after brain death. The Iranian supreme legislative body has approved organ donation from brain-dead patients if they gave permission for donation when they were alive. This permission is acceptable in both forms of written or verbal will (30). However, verbal will (wasiyat) requires special conditions, such as consent of the legal guardians, lack of explicit refusal of the deceased patient, and the intention of preventing harm to individuals in need of organs (31). In the present case, it can be analogously concluded that the patient's blood sample can be used for genetic testing with the consent of the first-degree family members to prevent harm to them.

Post-mortem use of genetic data and samples for research

Obtaining informed consent is still pivotal for protecting participants' rights in a research project. Few ethical guidelines regarding genetic research have explicitly determined the researcher's duty after the death of a participant (32). Tasse et al. showed that only 4 out of 24 documents related to biobanking research indirectly addressed the re-use of samples in case of a participant's death (32). On the contrary, a review of the literature published on the post-mortem use of genetic data for research by Bak et al. showed that reusing previously collected data for research was highly accepted among family members (3).

In 2003, The European Society of Human Genetics (ESHG) declared that reusing stored samples for research purposes required re-consent. Therefore, if the donor has died, only the ethics committee is authorized to permit the reuse of samples for research purposes based on the notion of minimum risk for the donor. If the donor has not explicitly illustrated his wishes (through a written informed consent), the ethics committee should permit the use of deceased donor's sample since the risk for

the subject is no more an issue. Therefore, the ESHG recommendations state that when individuals have restricted the use of their sample when they are still alive, these restrictions also apply after their death (33).

The Helsinki Declaration (2008 and 2013 versions) states that the research sample must be reused with informed consent. If obtaining consent is impossible (donor's death can be considered as an impossible situation), the secondary use of samples is possible only by an ethics committee's approval (34).

Although some studies emphasize altruistic aspects of consent for reusing samples for research purposes, the ethical guidelines and policies on research have to explicitly express their position about the secondary use of samples in research after death. Donors must decide about it when they are giving consent (3).

Conclusion

The controversy among experts about the concept of consent regarding the disclosure of genetic information and the reuse of genetic samples requires a definite solution. It also imposes significant ethical challenges in medical practice. Clinicians are generally recommended to discuss the importance of genetic information of the other members of the family with their patients requesting diagnostic or predictive genetic services. However, the matter is unclear in case of deceased patients and the prior refusal to share genetic information. The public should be informed about the shared ownership of genetic information and the notion of genetic consent. Finally, making decisions on a case-by-case basis is recommended in ethical conflicts.

The present case, we believe, has unique features. First, the patient's consent was obtained in an end-stage situation in the last days of his life. Second, the informed consent capacity assessment was not done, so the validity of the patient's consent is questioned. Third, re-use of the patient's sample leads to an earlier detection of the disease, better self-care, and greater attention to potential clinical manifestations for first-degree relatives.

Moreover, from an Islamic perspective, the validity of the patient's refusal is doubted after his death, as it cannot be considered a will[1] . Therefore, to prevent harm to the patient's family members, the patient's blood sample can be used for genetic

[1] *For more details about the concept of will in Islam, please read: Tripathi AK. THE CONCEPT OF 'WILL' UNDER MUSLIM LAW: A STUDY. http://ijlljs.in/the-concept-of-will-under-muslim-law-a-study/*

testing with the consent of the first-degree family members.

The risk-benefit assessment is the essential component of decision-making in both introduced approaches. According to beneficence and non-maleficence, the relatives' right to know, and kinship ethics, disclosing information to the first-degree relatives and re-use of the patient's sample are justifiable. In fact, it is not possible to consider explicit preventive and curative benefits for relatives, but reducing their psychological stress can be regarded as a benefit if they are entirely informed about the cost of genetic tests and the applicability of genetic test data.

The present scenario demonstrated a positive benefit-risk balance in which the benefits outweigh the risks. Therefore, it can be concluded that re-use of the patient's sample may be ethically justified in the presented case if the first-degree family members insist on genetic testing and are comprehensively informed about the benefits and harms.

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Reference:

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