VOLUME 31 · NUMBER 15 · MAY 20 2013

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Ethical, Legal, and Counseling Challenges Surrounding the Return of Genetic Results in Oncology

Martijn P. Lolkema, Christa G. Gadellaa-van Hooijdonk, Annelien L. Bredenoord, Peter Kapitein, Nancy Roach, Edwin Cuppen, Nine V. Knoers, and Emile E. Voest

Martijn P. Lolkema, Christa G. Gadellaa-van Hooijdonk, Annelien L. Bredenoord, Edwin Cuppen, Nine V. Knoers, and Emile E. Voest, University Medical Center Utrecht; Edwin Cuppen, Royal Netherlands Academy of Arts and Sciences, Utrecht; Peter Kapitein, Inspire2Live, Amsterdam, the Netherlands; and Nancy Roach, Fight Colorectal Cancer, Alexandria, VA.

Published online ahead of print at www.jco.org on April 15, 2013.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Emile E. Voest, MD, PhD, Department of Medical Oncology, F02.126, University Medical Center Utrecht, PO Box 85500, 3508 GA Utrecht, the Netherlands; e-mail: e.e.voest@umcutrecht.nl.

0732-183X/13/3115w-1842w/$20.00

DOI: 10.1200/JCO.2012.45.2789

ABSTRACT

In the last decade, an overwhelming number of genetic aberrations have been discovered and linked to the development of treatment for cancer. With the rapid advancement of next-generation sequencing (NGS) techniques, it is expected that large-scale DNA analyses will increasingly be used to select patients for treatment with specific anticancer agents. Personalizing cancer treatment has many advantages, but sequencing germline DNA as reference material for interpreting cancer genetics may have consequences that extend beyond providing cancer care for an individual patient. In sequencing germline DNA, mutations may be encountered that are associated with increased susceptibility not only to hereditary cancer syndromes but also to other diseases; in those cases, disclosing germline data could be clinically relevant and even lifesaving. In the context of personal autonomy, it is necessary to develop an ethical and legal framework for how to deal with identified hereditary disease susceptibilities and how to return the data to patients and their families. Because clear legislation is lacking, we need to establish guidelines on disclosure of genetic information and, in the process, we need to balance privacy issues with the potential advantages and drawbacks of sharing genetic data with patients and their relatives. Importantly, a strong partnership with patients is critical for understanding how to maximize the translation of genetic information for the benefit of patients with cancer. This review discusses the ethical, legal, and counseling issues surrounding disclosure of genetic information generated by NGS to patients with cancer and their relatives. We also provide a framework for returning these genetic results by proposing a design for a qualified disclosure policy.

J Clin Oncol 31:1842-1848. © 2013 by American Society of Clinical Oncology

INTRODUCTION

The advent of highly efficient DNA sequencing techniques has the potential to transform our understanding of the genotype-phenotype correlations that underlie many if not all human diseases. For oncologists and for patients with cancer, this advance offers a unique opportunity to facilitate a better selection of patients for a specific treatment because somatic genetic changes may profoundly affect response to systemic anticancer therapy. Next-generation sequencing (NGS)—a rapidly expanding field of research on techniques that can be used to interrogate the cancer genome—has the promise of personalizing treatment for patients with cancer. The last decade saw a significant increase in the development of drugs that specifically target genetic aberrations. In parallel, simple genotyping techniques for these targets, such as testing for single nucleotide variation (in *BRAF*[1] and *c-KIT*[2]) or structural variation (*BCR-ABL* translocations,[3] *ALK* rearrangements,[4] or overexpression of specific proteins such as *HER2*[5]), became available. But now we enter a new era in which we will have access to information encompassing the patient's whole exome or even whole genome. It is important to realize that the variation in germline DNA between individuals is overwhelming, with up to 5 million single nucleotide variants genome-wide[6] and many thousands of structural variants affecting an even larger number of bases.[7] This enormous germline variation between individuals hinders our ability to determine relevant somatic mutations in tumors. To circumvent this problem, it is common for studies using NGS to compare germline DNA with cancer DNA to filter out true somatic mutations. However, because germline DNA contains unique personal information, not just information relevant to the disease under study, other sensitive issues such as risk of developing cancer[8] or the risk of developing other diseases or conditions such as neurologic or psychiatric illnesses[9] are encountered more often. These findings may have an impact not only on the individual patient but also on immediate family members. Clearly, this raises many challenges. This review provides an overview of the ethical, legal, and

counseling issues surrounding the return of genetic data to patients with cancer. We have involved patients because their input will be crucial to maximizing the translation of genetic information for the benefit of patients with cancer. Finally, we propose a framework for returning genetic results in oncology that may support future studies.

EMERGING ETHICAL DUTY TO RETURN GENETIC RESULTS

The question of whether and to what extent genetic research results should be returned to research participants has become one of the most urgent and extensively debated ethical issues in genetics.[10] This debate has taken place mainly in the research context, but it is also relevant for clinical applications of NGS, and it demands continuous attention now that NGS is entering the "clinical genomics" arena, particularly in the field of cancer care.[11] Here, we refer to genetic research results as a collective term, but it is important to be aware of the distinction between research findings and incidental findings (which may better be referred to as "unsolicited findings"[12]). Although both relate to an individual person, a genetic research finding is generated in a specific study context: it is a confirmation of a sought for genetic variant. By contrast, incidental findings are unintended and beyond the aims of a study.[13] Clearly, the latter will pose counseling challenges because patients with cancer may be confronted not only with cancer susceptibility syndromes but also with genetic risk factors associated with completely different disorders such as dementia and Parkinson's disease. The wider the scope of a genetic test, the more likely the generation of such by-products will be.

The debate on whether to reveal genetic research results to study participants has been dynamic, and various opposing viewpoints have been expressed (reviewed in Bredenoord et al[14]). However, the extreme positions from nondisclosure to full disclosure are seldom defended. At one end of the spectrum, full disclosure is considered by the majority of commentators to be undesirable and nonsensical at best, because it suggests disclosure of all raw sequencing data (reviewed in Bredenoord et al[14]). It has recently been argued that full disclosure will become feasible and the right thing to do in a landscape of decreasing costs of sequencing, increasing use of social media, and support of patient initiatives.[15] At the other end of the spectrum, it has been argued that nondisclosure is unethical because it ignores the widely recognized duty to warn someone when their life is threatened and serious harm can be avoided. Therefore, many, if not most, accept that there is, at a minimum and in certain contexts, a duty to return lifesaving genetic data. And although genetics researchers are still divided on this issue, there now seems to be growing support for the view that at least some genetic results should be communicated to research participants.[10,16-18] This emerging duty to return genetic information is usually on the basis of autonomy, beneficence, and the acknowledgment that translational genomics research cannot progress without the engagement and involvement of research participants and the patient community.[19]

First, respect for the autonomy of study participants and patients alike warrants disclosure of genetic results, provided they want to receive them. Genetic research results may help people take control of their life, realize or adjust life plans, or revise their strategies for coping.[20] Indeed, research participants, the patient advocacy community, and the general public have explicitly expressed an interest in receiving such results. Focus group interviews that examined public perceptions revealed that a majority of the public believes that any research protocol should adopt provisions for the return of individual research results. In one study, participants understood that factors such as uncertainty about the effect of mutations and limited resources of the researchers could be valid reasons for limiting the amount of data returned, but they also acknowledged the importance of patient education.[21] This notion has been confirmed by a study that used psychoeducation to affect patient attitude regarding participation in clinical trials.[22] In addition, it is important for the families of patients with cancer to be informed about whether they are exposed to a hereditary risk of cancer.

Research into the motivations of patients and their relatives (to undergo and receive the results of genetic testing) has been performed in diseases such as colorectal cancer that could be prevented by screening. Retrospective analysis revealed that among 45 patients with colorectal cancer and 102 of their first-degree relatives, 95% reported willingness to receive genetic information.[23] In a larger cohort study coordinated by The Johns Hopkins Hospital, relatives of patients with colorectal cancer were surveyed, and 77.4% of 1,217 respondents were willing to undergo genetic testing.[24] In a separate study of the motivations of colorectal cancer survivors for undergoing genetic testing, the main factors affecting their choices were determining the cancer risk of family members, improving research, and determining the need for screening.[25] These data suggest that a significant proportion of patients with cancer and their relatives want to be informed about genetic data that affect their cancer risk. Whether patients with cancer and their families want to be informed about their risk of other diseases remains to be determined and requires further research.

Second, beneficence warrants disclosure, provided the results are clinically and analytically valid, useful, and actionable[13]and also that meaningful options are available, such as prevention, avoidance of deterioration, treatment, and potential to adjust life plans or strategies for coping. Genetic tests have improved our ability to prevent cancer. For example, mutations in the *RET* oncogene result in medullary thyroid cancer in young children; in this case, genetic testing would enable lifesaving prophylactic thyroidectomy.[26] Similarly, genetic germline aberrations in the *BRCA* genes strongly predispose to breast and ovarian cancer. Carriers of *BRCA1* and *BRCA2* mutations are offered prophylactic surgery to prevent development of (further) cancers and/or close surveillance to aid early detection of cancers.[27-29] In the years to come, NGS-based genetic testing will likely contribute significantly to the identification of additional germline genetic aberrations that may have potentially harmful consequences. In summary, feedback of genetic results may improve the health of patients with cancer (or avoid deterioration), positively affect their quality of life, stimulate them to adjust life plans and coping strategies, and prevent illness in their family members.

Third, offering the possibility of feedback of genetic results may engage and educate research participants. Feedback provides an acknowledgment that translational genomics research cannot progress without active contributions from research participants and the patient community. Empirical studies suggest that patients participate in genetic cancer research partly because they expect therapeutic benefit and partly for altruistic reasons.[30] Focus group studies in healthy research participants reveal that most participants expect some form of reciprocity (eg, in the form of return of results), especially if they anticipate some form of benefit for themselves or their families.[21,31-33]

Table 1. Disclosure of Genetic Information in Oncology

Benefit	Content	Consent	Return Policy
Clear	Life-threatening conditions (cancer susceptibility syndromes and information with paramount clinical utility [ie, conditions that can be either prevented or treated or influence reproductive decision making])	Default is to return; however, opt-out is offered	Default package
Possible	Potential or moderate clinical or reproductive benefit (eg, conditions for which interventions are unsatisfactory)	Opt in	Package 2
Unlikely	No clear clinical utility (eg, not directly influencing either health or reproduction)	Opt in	Package 3
Unknown	Unclassified variants	—	No disclosure

NOTE. Adapted from Bredenoord et al[19] and Bredenoord and Van Delden.[36]

There is a call for more active partnering between patients and researchers in developing and disclosing research findings.[34] There is a lack of studies that investigate the preferences and expectations of patients with cancer toward return of genetic results that focus on information beyond the realm of malignant disease risk, which is important in view of the normative component of result selection and the feasibility of any feedback policy.

WHAT SUBSETS OF GENETIC FINDINGS SHOULD BE RETURNED IN ONCOLOGY?

Although there is a growing consensus that genetic findings should be offered for disclosure, considerable controversy remains over which findings warrant an offer of return and also to whom. Thus far, there is no specific list of which genetic and genomic findings should be eligible for disclosure to patients.[10]

Genetic risk information can be relevant to a patient's family members. Participants' relatives, like the participants themselves, may have a legitimate interest in receiving some results or at least having access to them. This issue becomes especially salient when the participant has passed away, which is not uncommon in studies involving patients with cancer. Thus, postmortem disclosure to a research participant's relatives should at least be foreseen and agreed on during inclusion, because there is no possibility of asking permission for disclosing data to relatives after a patient has passed away.[35,36]

Although there are valid reasons for assuming a moral duty to return certain genetic information in oncology, competing considerations should also be taken into account, such as the limitations of autonomous decision making, counseling challenges, risks of disclosure for the individual person (and her family members), and risks of unduly hindering biomedical research.

The basis for every study and clinical treatment is a valid informed consent procedure, which adds to the patients' understanding of the purpose of the study or treatment and the results the study may generate.[19] However, in the era of NGS-based genetic results, obtaining true informed consent, in which the patient foresees all consequences of study participation, is becoming increasingly difficult because informing patients about all potential repercussions of potential outcomes is virtually impossible. Moreover, the determination of whether results are useful or valuable is not merely a scientific or clinical judgment but a normative judgment as well. A qualified disclosure policy in which patients are given qualified choices (Table 1, modified from Bredenoord et al[19] and Wolf et al[37]) is one approach that takes into account the ever-changing landscape of genetic analyses, the autonomy of the patient (and the difficulties people have in making a reasonable selection on what to receive from the wide array of genetic information), and the normative component of result selection. Indeed, a randomized trial comparing the value of different types of informed consent in genetic trials showed that tiered informed consent is more likely to respect the preferences of individual patients.[38] In a qualified disclosure policy, several packages of genetic results are offered. By working with a predefined menu of options, we both respect the autonomy of the patients/participants and acknowledge that we need to limit the amount of choices they need to make. The next step, then, is to refine the design of these packages and determine what information is appropriate to add in the context of cancer.

DESIGNING A QUALIFIED DISCLOSURE POLICY IN ONCOLOGY

There are several well-defined cancer susceptibility syndromes (Table 2, modified from the Netherlands Foundation for the Detection of Hereditary Tumours[39]) that could serve as starting point for cancer-oriented researchers to use in determining which germline genetic results are eligible for communicating to patients. The syndromes in Table 2 have been well characterized and represent a collection of genotype-phenotype correlations with defined clinical consequences. Moreover, the genetic counseling community has defined adequate tests and counseling strategies to address these aberrations. Results regarding the diseases described in Table 2 could thus be offered as the default package returned to patients and their families after participating in NGS-based studies, unless they actively decide to opt out of receiving results (Table 1). The content of this default package should be determined on the basis of solid science and should include annotation initiatives such as the ENIGMA international consortium for *BRCA* variants, which can help determine the mutations that should be reported.[40,41]

Genetic sequencing often generates information about diseases beyond the field of cancer. Funding agencies strongly encourage the deposition of sequencing results in large databases because they are trying to optimize the return on investment of this type of large-scale research.[42] The rate of detecting disease-causing or disease-enhancing variants for developing schizophrenia, diabetes, dementia, and a whole range of diseases will generally be low but might be clinically significant—a phenomenon that has already been encountered in the Clinseq project, a large population-based genomics initiative in which healthy individuals donate their DNA for sequencing and agree to phenotypic follow-up.[11] The oncology community is now being challenged to develop a strategy for returning genetic risk data on nonmalignant diseases.

Table 2. Germline Mutations Associated With Cancer Susceptibility Syndromes

Cancer Syndrome	Gene	Chromosome	Main Clinical Features*
Hereditary breast/ovarian cancer	*BRCA1*	17	Early-onset breast and ovarian cancers
	BRCA2	13	
Li-Fraumeni syndrome	*TP53*	17	Different types of sarcomas, early-onset breast cancer, brain tumors, and adrenocortical cancer
Cowden syndrome	*PTEN*	10q23	Breast cancer, thyroid cancer, dysplastic gangliocytoma of the cerebellum, and endometrial cancer
Lynch syndrome	*MSH2*	2	Colon cancer risk from flat polyps with microsatellite instability, endometrial cancer in females, wide variety of tumors at other sites
	MLH1	6	
	MSH6	2	
	PMS2	7	
	EPCAM (deletion)	2	
Familial adenomatous polyposis	*APC*	5	Multiple colon polyps, colorectal cancer, duodenal cancer, desmoid tumors
	MUTYH	1	
Peutz-Jeghers syndrome	*STK11*	19	Multiple hamartomas, breast cancer, colorectal cancer, pancreatic cancer, gastric cancer, and increased risk for other tumors
Hereditary diffuse gastric cancer	*CDH1*	16	Gastric cancer and breast cancer
Familial atypical multiple mole melanoma	*CDKN2A*	9	Melanoma and pancreatic adenocarcinomas and cerebral astrocytomas
	CDK4	12	
Multiple endocrine neoplasia type 1	*MEN1*	11	Neuroendocrine tumors of pancreas, pituitary tumors, adrenal adenomas, and neuroendocrine tumors arising from stomach, lungs, or thymus
Multiple endocrine neoplasia type 2	*MEN2A*	10	Medullary thyroid cancer, pheochromocytoma and hyperparathyroidism
	MEN2B	10	
	RET	10	
Familial paraganglioma	*SDHD*	11	Paragangliomas and pheochromocytomas
	SDHB	1	
	SDHC	1	
Von Hippel-Lindau disease	*VHL*	3	Renal cell carcinoma, hemangioblastomas, and pheochromocytomas
Birt-Hogg-Dubé syndrome	*FLCN*	17p11.2	Chromophobe renal carcinoma
Tuberous sclerosis syndrome	*TSC1*	9q34	Angiofibromas, angiomyolipomas, and giant cell astrocytomas
	TSC2	16p13	
Neurofibromatosis type 1	*NF1*	17	Optic gliomas, neurofibromas with potential malignant degeneration
Neurofibromatosis type 2	*NF2*	2	Schwannomas, meningeomas, gliomas, and neurofibromas
Gorlin syndrome	*PTCH1*	9	Childhood primitive neuroectodemal tumors (PNET) and frequent skin basal cell carcinomas
Juvenile polyposis syndrome	*BMPR1A*	10	Multiple polyps in colon at young age
	SMAD4	18	

NOTE. Lifetime risks of cancer susceptibility syndromes differ according to the affected gene and the specific mutation found. This table lists genes that harbor known disease-causing mutations.
*Only oncology-related features are represented in this table.

PRIVACY AND DATA SHARING IN THE ERA OF LARGE-SCALE GENOMIC DATA

The Declaration of Helsinki and the Good Clinical Practice (GCP) code laid down a governance framework that aimed to protect the patient's interest and privacy in conventional therapeutic trials. Adherence to GCP ensures, among other things, a patient's privacy. Privacy can be defined as "an individual's personal autonomy that makes him master of all those facts about his own identity."[43] Genomics research has the potential to threaten that privacy by analyzing and exposing sensitive data regarding the presence or absence in a research cohort, ancestry, or relatedness (eg, paternity).[44] For patients with cancer, analyzing the cancer genome could reveal the mechanism of cancer development such as a history of smoking or sun exposure.[45,46] Indeed, recent data show that by using databases from the Genome-Wide Association Study (GWAS), individuals could be identified, even in highly complex mixtures of DNA, if a reference sample was available.[47-51] Transferring these data to third parties such as family, community members, or insurance companies may potentially harm the privacy of research participants.[52] In contrast, the research community and society in general encourage sharing of genomic data as a way to use available resources more efficiently. The Human Genome Project and subsequent collaborations such as the 1000 Genomes Project are funded on the premise that publicly sharing genomic data will catalyze research and progress in the medical sciences. But with these data available in the public domain, the risk to privacy is a growing concern.[43,53]

Within the framework of clinical trials, most people are willing to share their data for appropriate research uses in exchange for specific guarantees of de-identification. However, NGS data can often be traced back to an individual, depending on how much data has been collected. The real value of genetic data is in the connection between the genetic and clinical data for the same patient. Interestingly, a recent study shows that concerns about privacy of research participants is perceived by the public as an important yet overseeable issue that should not form obstacles to obtaining novel scientific insight.[53] Studies on the perception of biobanks

show that the public views biobanking as an important research resource, and up to 60% of the general public is willing to contribute data and tissue.[54] But participants want to be acknowledged, and they feel that their consent should be required if data are shared beyond the control of the initial investigators (eg, if the data are included in the database for Genotypes and Phenotypes [dbGaP], a central US database).[42,55] A common theme in research on privacy is the trust research participants have in a research institution and their reluctance to have their genomic data exposed outside the research community to insurance companies or other for-profit organizations.[42,55] In summary, genomics research poses new risks in the fields of data protection and medical confidentiality. Protection of privacy is key to keeping the public's trust, and it needs to be considered when designing strategies for returning genetic results.

LEGAL GUIDANCE ON RETURNING GENETIC RESULTS

Returning genetic results has an important legal dimension, especially when those result affect family members of patients and research participants.[56] Most countries have laws that cover patient-physician confidentiality, but this confidentiality is not absolute. Patients may authorize a physician to convey medical information to third parties and, in some circumstances, the law mandates the release of medical information for use in judicial proceedings or to protect others from harm (eg, in the case of transmissible diseases, child abuse, domestic violence, or conditions that constitute a danger for public safety).[56] A topic of discussion is whether conferring genetic data related to hereditary cancer syndromes to family members may be part of the latter exception to the patient-physician confidentiality laws. Claims for negligence have been brought against US physicians, which provides some insight into the attitude of US courts on the responsibility of physicians toward family members of patients with hereditary syndromes. When a physician knows that a certain condition is heritable and knows that there are relatives who may be affected, the physician is obligated to warn the patient of such risk. In the case of Pate *v* Threlkel, the Florida (US) Supreme Court ruled that after genetic testing, the physician has an obligation to warn the patient that his or her family is at risk.[57] Shortly thereafter, in the case of Safer *v* Estate of Pack, the New Jersey (US) Supreme Court refined this interpretation with specific conditions under which family members at risk should be warned, even after the death of the patient.[58] In a third case, Molloy *v* Meier, the Minnesota (US) Supreme Court acknowledged that medical geneticists have a responsibility to convey adequate information to relatives regarding serious reproductive risks.[59] In the future, similar cases will likely also be litigated outside the United States, and cultural differences toward the legal status of personal genetic information will become apparent. Importantly, these cultural differences may have an impact on the development of global genetic data-sharing initiatives. These legal proceedings have led the American Society of Human Genetics to adjust its point of view on determining which serious conditions require disclosure of genetic information to affected family members.[60] The American Society of Clinical Oncology has not changed its view and states that the main concern is to safeguard the privacy of patients, meaning that physicians should not report genetic data to relatives without the patient's consent.[61,62] In fact, a study among medical geneticists concerning the refusal of patients to inform their relatives showed that medical geneticists seriously considered informing the relatives themselves for 25% of all patients refusing to inform their relatives, but only four of 123 medical geneticists actually did so.[63] The issue of reporting genetic results to relatives remains difficult. Apart from the legal cases just described, no explicit laws cover how to return results of genetic tests to relatives. Therefore, researchers and physicians will need to balance individual cases by using the existing guidelines.

Another potential legal complication of returning or sharing genetic results is the legislation on privacy. In the United States, the Genetic Information Nondiscrimination Act (GINA) forbids insurance companies to discriminate through reduced coverage or increased prices for coverage and prohibits employers from making adverse employment decisions on the basis of a person's genetic code.[64] This is an important step toward unlocking the full potential of personalized medicine because it neutralizes the fear of being discriminated against because of genetics. In response to the recent developments in large-scale genetic testing, the

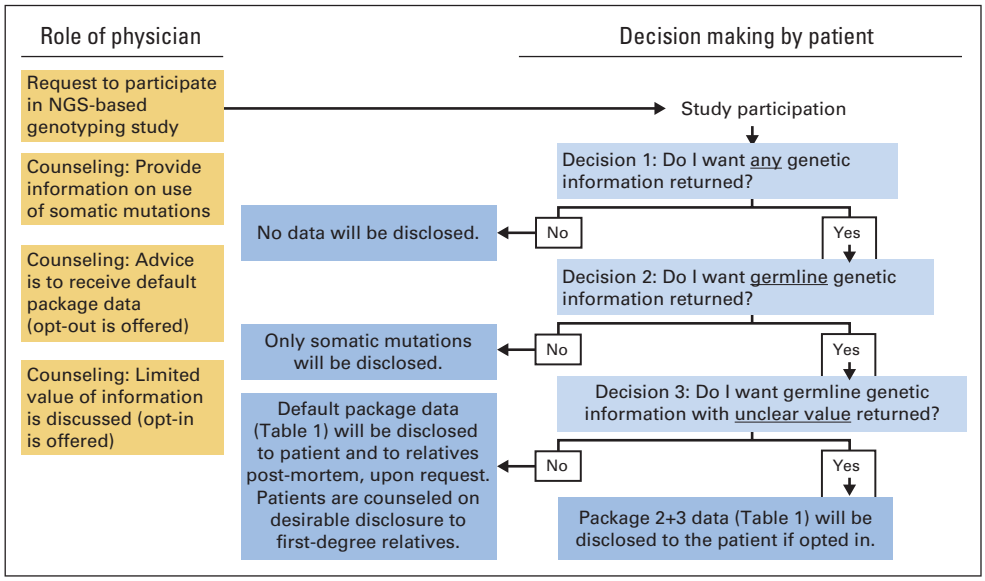

Fig 1. Return of genetic results in oncology: Patient-oriented flow chart on tiered consent. This figure depicts the flow of questions asked of patients when using a tiered consent strategy in oncology. The right panels show the questions we ask patients sequentially and the left panel depicts the counseling tasks the physician will have to complete to help patients to make their choice. NGS, next-generation sequencing.

European Union has published a document drafted by the Council of Europe with a similar purpose of protecting against discrimination because of genetics. However, it remains a guideline/protocol and has not yet been turned into legislation.[65]

PATIENTS' PERSPECTIVES ON THE ETHICAL AND LEGAL ISSUES OF RETURNING GENETIC RESULTS

To develop guidelines on how to return genetic data to patients with cancer and to the community, it is critical to create partnerships with patients and patient advocates (Appendix Table A1, online only). Active involvement of the patient community is essential for advancing the debate on how to return genetic results in oncology. In shaping the framework for returning genetic results to patients, we feel that it is important to involve all relevant stakeholders: medical oncologists, ethicists, clinical and molecular geneticists, policy makers, insurance companies and, most importantly, patients and patient advocates. These stakeholders should be involved in ongoing discussions to guide transmission of NGS results from purely scientific endeavors toward clinical applications.

MOVING FORWARD: DESIGNING A QUALIFIED DISCLOSURE POLICY

Support is growing for the idea of communicating at least some genetic results to patients and research participants. In view of this emerging duty to return genetic information, it is no longer a matter of whether results should be fed back, but rather which results should be fed back. Here, we propose a feedback policy that includes predefined packages of information as a way of returning results to patients with cancer. This could serve as the basis for further refining and shaping of this framework and allocating potential genetic mutations to the packages. The process of informed consent using a tiered consent proposal makes it easier to define those genetic mutations that are truly actionable (Table 2). Moreover, it allows us to define the categories of mutations that have a predefined impact on patients and to counsel patients accordingly (Fig 1 and Table 1). With the limited life expectancy of a large part of the population of patients with cancer, there is also a question of whether we have an obligation to return results to relatives post mortem. We propose to inform patients and family members that relatives have the option of contacting researchers and treating physicians to learn about truly actionable germline mutations after the patient has passed away. Leaving the initiative with the relatives respects the rights of those who do not want to know and, at the same time, permits the transfer of vital information to relatives who do want to know. In this proposition, it is essential that the patient does not opt out of receiving results and is prompted to discuss genetic testing results with his or her family.

CONCLUSION

There are numerous challenges ahead for maximizing the use of genetic information in the prevention or treatment of cancer. Sequencing technology is no longer the rate-limiting step. Ethical, legal, and counseling issues need continuous attention. Partnerships of scientists, clinicians, and patients are essential for generating guidelines for the return of genetic results to patients and their relatives. In this overview, we have provided a framework that may serve as a starting point for future studies that incorporate genomic data into clinical cancer research.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
Employment or Leadership Position: Nancy Roach, Fight Colorectal Cancer (U) **Consultant or Advisory Role:** None **Stock Ownership:** None **Honoraria:** None **Research Funding:** None **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Martijn P. Lolkema, Christa G. Gadellaa-van Hooijdonk, Annelien L. Breedenoord, Nine V. Knoers, Emile E. Voest
Administrative support: Christa G. Gadellaa-van Hooijdonk
Collection and assembly of data: Martijn P. Lolkema, Christa G. Gadellaa-van Hooijdonk, Annelien L. Breedenoord, Peter Kapitein, Nancy Roach, Emile E. Voest
Data analysis and interpretation: Martijn P. Lolkema, Christa G. Gadellaa-van Hooijdonk, Annelien L. Breedenoord, Edwin Cuppen, Emile E. Voest
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Sosman JA, Kim KB, Schuchter L, et al: Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. N Engl J Med 366:707-714, 2012
2. Heinrich MC, Corless CL, Demetri GD, et al: Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol 21:4342-4349, 2003
3. Druker BJ, Sawyers CL, Kantarjian H, et al: Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. N Engl J Med 344:1038-1042, 2001
4. Kwak EL, Bang YJ, Camidge DR, et al: Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 363:1693-1703, 2010
5. Slamon DJ, Leyland-Jones B, Shak S, et al: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 344:783-792, 2001
6. Gonzaga-Jauregui C, Lupski JR, Gibbs RA: Human genome sequencing in health and disease. Annu Rev Med 63:35-61, 2012
7. Girirajan S, Campbell CD, Eichler EE: Human copy number variation and complex genetic disease. Annu Rev Genet 45:203-226, 2011
8. Johnston JJ, Rubinstein WS, Facio FM, et al: Secondary variants in individuals undergoing exome sequencing: Screening of 572 individuals identifies high-penetrance mutations in cancer-susceptibility genes. Am J Hum Genet 91:97-108, 2012
9. Hoge SK, Appelbaum PS: Ethics and neuropsychiatric genetics: A review of major issues. Int J Neuropsychopharmacol 15:1547-1557, 2012
10. Wolf SM: The past, present, and future of the debate over return of research results and incidental findings. Genet Med 14:355-357, 2012
11. Biesecker LG: Opportunities and challenges for the integration of massively parallel genomic sequencing into clinical practice: Lessons from the ClinSeq project. Genet Med 14:393-398, 2012

12. Schmidtke J, Cassiman JJ: The EuroGentest clinical utility gene cards. Eur J Hum Genet 18:1068, 2010

13. Isasi R, Knoppers BM, Andrews PW, et al: Disclosure and management of research findings in stem cell research and banking: Policy statement. Regen Med 7:439-448, 2012

14. Bredenoord AL, Kroes HY, Cuppen E, et al: Disclosure of individual genetic data to research participants: The debate reconsidered. Trends Genet 27:41-47, 2011

15. Angrist M: You never call, you never write: Why return of 'omic' results to research participants is both a good idea and a moral imperative. Per Med 8:651-657, 2011

16. [No authors listed]: Incidental benefits. Nature 483:373, 2012

17. Hayden EC: DNA donor rights affirmed. Nature 483:387, 2012

18. National Heart, Lung, and Blood Institute working group, Fabsitz RR, McGuire A, et al: Ethical and practical guidelines for reporting genetic research results to study participants: Updated guidelines from a National Heart, Lung, and Blood Institute working group. Circ Cardiovasc Genet 3:574-580, 2010

19. Bredenoord AL, Onland-Moret NC, Van Delden JJ: Feedback of individual genetic results to research participants: In favor of a qualified disclosure policy. Hum Mutat 32:861-867, 2011

20. Ormond KE, Wheeler MT, Hudgins L, et al: Challenges in the clinical application of whole-genome sequencing. Lancet 375:1749-1751, 2010

21. Bollinger JM, Scott J, Dvoskin R, et al: Public preferences regarding the return of individual genetic research results: Findings from a qualitative focus group study. Genet Med 14:451-457, 2012

22. Jacobsen PB, Wells KJ, Meade CD, et al: Effects of a brief multimedia psychoeducational intervention on the attitudes and interest of patients with cancer regarding clinical trial participation: A multicenter randomized controlled trial. J Clin Oncol 30:2516-2521, 2012

23. Ceballos RM, Newcomb PA, Beasley JM, et al: Colorectal cancer cases and relatives of cases indicate similar willingness to receive and disclose genetic information. Genet Test 12:415-420, 2008

24. Petersen GM, Larkin E, Codori AM, et al: Attitudes toward colon cancer gene testing: Survey of relatives of colon cancer patients. Cancer Epidemiol Biomarkers Prev 8:337-344, 1999

25. Esplen MJ, Madlensky L, Aronson M, et al: Colorectal cancer survivors undergoing genetic testing for hereditary non-polyposis colorectal cancer: Motivational factors and psychosocial functioning. Clin Genet 72:394-401, 2007

26. Lips CJ, Landsvater RM, Höppener J, et al: Clinical screening as compared with DNA analysis in families with multiple endocrine neoplasia type 2A. N Engl J Med 331:828-835, 1994

27. Meijers-Heijboer H, van Geel B, van Putten WL, et al: Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med 345:159-164, 2001

28. Domchek SM, Friebel TM, Singer CF, et al: Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA 304:967-975, 2010

29. Hoover DJ, Paragi PR, Santoro E, et al: Prophylactic mastectomy in high risk patients: A practice-based review of the indications—Do we follow guidelines? Breast Dis 31:19-27, 2010

30. Hallowell N, Cooke S, Crawford G, et al: An investigation of patients' motivations for their participation in genetics-related research. J Med Ethics 36:37-45, 2010

31. Murphy J, Scott J, Kaufman D, et al: Public expectations for return of results from large cohort genetic research. Am J Bioeth 8:36-43, 2008

32. Wendler D, Emanuel E: The debate over research on stored biological samples: What do sources think? Arch Intern Med 162:1457-1462, 2002

33. Dixon-Woods M, Ashcroft RE, Jackson CJ, et al: Beyond "misunderstanding": Written information and decisions about taking part in a genetic epidemiology study. Soc Sci Med 65:2212-2222, 2007

34. Fisher R: A closer look revisited: Are we subjects or are we donors? Genet Med 14:458-460, 2012

35. Chan B, Facio FM, Eidem H, et al: Genomic inheritances: Disclosing individual research results from whole-exome sequencing to deceased participants' relatives. Am J Bioeth 12:1-8, 2012

36. Bredenoord AL, van Delden JJ: Disclosing individual genetic research results to deceased participants' relatives by means of a qualified disclosure policy. Am J Bioeth 12:10-12, 2012

37. Wolf SM, Lawrenz FP, Nelson CA, et al: Managing incidental findings in human subjects research: Analysis and recommendations. J Law Med Ethics 36:219-248, 211, 2008

38. McGuire AL, Oliver JM, Slashinski MJ, et al: To share or not to share: A randomized trial of consent for data sharing in genome research. Genet Med 13:948-955, 2011

39. Netherlands Foundation for the Detection of Hereditary Tumours (STOET), Dutch Society for Clinical Genetics (VKGN): Erfelijke tumoren: Richtlijnen voor diagnostiek en preventie. (Hereditary cancer syndromes: Guidelines for diagnosis and prevention), 2010

40. Spurdle AB, Healey S, Devereau A, et al: ENIGMA: Evidence-based network for the interpretation of germline mutant alleles—An international initiative to evaluate risk and clinical significance associated with sequence variation in BRCA1 and BRCA2 genes. Hum Mutat 33:2-7, 2012

41. Radice P, De Summa S, Caleca L, et al: Unclassified variants in BRCA genes: Guidelines for interpretation. Ann Oncol 22:i18–i23, 2011 (suppl 1)

42. Ludman EJ, Fullerton SM, Spangler L, et al: Glad you asked: Participants' opinions of r-consent for dbGap data submission. J Empir Res Hum Res Ethics 5:9-16, 2010

43. Kaye J: The tension between data sharing and the protection of privacy in genomics research. Annu Rev Genomics Hum Genet 13:415-431, 2012

44. Johnson AD, Leslie R, O'Donnell CJ: Temporal trends in results availability from genome-wide association studies. PLoS Genet 7:e1002269, 2011

45. Pleasance ED, Stephens PJ, O'Meara S, et al: A small-cell lung cancer genome with complex signatures of tobacco exposure. Nature 463:184-190, 2010

46. Pleasance ED, Cheetham RK, Stephens PJ, et al: A comprehensive catalogue of somatic mutations from a human cancer genome. Nature 463:191-196, 2010

47. Homer N, Szelinger S, Redman M, et al: Resolving individuals contributing trace amounts of DNA to highly complex mixtures using high-density SNP genotyping microarrays. PLoS Genet 4:e1000167, 2008

48. Im HK, Gamazon ER, Nicolae DL, et al: On sharing quantitative trait GWAS results in an era of multiple-omics data and the limits of genomic privacy. Am J Hum Genet 90:591-598, 2012

49. Sankararaman S, Obozinski G, Jordan MI, et al: Genomic privacy and limits of individual detection in a pool. Nat Genet 41:965-967, 2009

50. Jacobs KB, Yeager M, Wacholder S, et al: A new statistic and its power to infer membership in a genome-wide association study using genotype frequencies. Nat Genet 41:1253-1257, 2009

51. Visscher PM, Hill WG: The limits of individual identification from sample allele frequencies: Theory and statistical analysis. PLoS Genet 5:e1000628, 2009

52. Gitter DM: The challenges of achieving open-source sharing of Biobank data. Biotechnology Law Report 29:623-635, 2010

53. Pullman D, Etchegary H, Gallagher K, et al: Personal privacy, public benefits, and biobanks: A conjoint analysis of policy priorities and public perceptions. Genet Med 14:229-235, 2012

54. Kaufman DJ, Murphy-Bollinger J, Scott J, et al: Public opinion about the importance of privacy in biobank research. Am J Hum Genet 85:643-654, 2009

55. McGuire AL, Hamilton JA, Lunstroth R, et al: DNA data sharing: Research participants' perspectives. Genet Med 10:46-53, 2008

56. Godard B, Hurlimann T, Letendre M, et al: Guidelines for disclosing genetic information to family members: From development to use. Fam Cancer 5:103-116, 2006

57. Pate *v* Threlkel. 661 So2d 278 (Fla 1995), 1995

58. Safer *v* Estate of Pack. 677 A2d 1188 (NJ Super Ct App Div 1996), 1996

59. Molloy *v* Meier. 679 NW 2d 711 (Minn. 2004), 2004

60. [No authors listed]: ASHG statement: Professional disclosure of familial genetic information—The American Society of Human Genetics Social Issues Subcommittee on Familial Disclosure. Am J Hum Genet 62:474-483, 1998

61. American Society of Clinical Oncology: American Society of Clinical Oncology policy statement update: Genetic testing for cancer susceptibility. J Clin Oncol 21:2397-2406, 2003

62. Robson ME, Storm CD, Weitzel J, et al: American Society of Clinical Oncology policy statement update: Genetic and genomic testing for cancer susceptibility. J Clin Oncol 28:893-901, 2010

63. Falk MJ, Dugan RB, O'Riordan MA, et al: Medical Geneticists' duty to warn at-risk relatives for genetic disease. Am J Med Genet A 120A:374-380, 2003

64. Feldman EA: The Genetic Information Nondiscrimination Act (GINA): Public Policy and Medical Practice in the Age of Personalized Medicine. J Gen Intern Med 2012. ssrn.com/abstract=2007233

65. Council of Europe: Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes: Article 4—Non-discrimination and non-stigmatisation. Strasbourg 27.XI. 2008

Appendix

Table A1. Patient Advocate Statements

The patient advocate view on our duty to return genetic data
Nancy Roach* states that "The return of actionable genetic information, whether it was sought for or found by chance, is an obvious benefit to patients and is, in fact, expected by many. Individual genetic data that is not actionable are more challenging and depend on patient preference and on the patient-physician relationship."
Peter Kapitein† states that "DNA sequencing will provide information about other diseases and we have to accept this. Information that also affects our relatives should be made available when our relatives ask for it. If genetic information cannot be acted upon, do not inform them because it will disturb their lives and happiness."
The patient advocate view on patient protection and privacy
Nancy Roach: "Patients are 'protected' by laws and regulations that require a risk/benefit analysis prior to the conduct of a clinical trial. The existing regulatory framework focuses largely on risk—on protecting patient safety while on trial—and protecting patient privacy. This framework has become increasingly bureaucratic and restrictive, leading to many efforts to bring 'common sense' back to clinical research. For example, the Office of Human Research Protection (OHRP) has proposed significant changes to the Common Rule which seek to minimize bureaucracy. However, there is little regulatory guidance on how to maximize the benefit to individuals on trial and the benefit to society as a whole."
Peter Kapitein confirms that "We are in a hurry; we want data about our specific type of cancer in our individual body. These data need to be shared because the only way to improve our understanding of how to cure cancer in a single patient is to know what happens in many. With so many cancer-related deaths, privacy is of limited concern."
The patient advocate view on the role of patients in advancing science
Nancy Roach states that "Regulations that require future consent for use of genetic information were enacted to protect patient privacy and misuse of data. However, in the real world, future consent is frequently not feasible. In that case, should the data provided by the patient on trial be locked away? Is that what the patients and their family members want? I suspect that the answer is not a binary yes/no. Tiered consents, as mentioned above, are one approach. A patient recently said to me 'I want the research system to make the best use of my data. I want them to study it and share it, and I want my children to benefit from the knowledge.' A rational regulatory framework must maximize the gift that trial participants give to society, through both minimizing risk and maximizing benefit."

*Nancy Roach serves as a member of the Board of Directors at Fight Colorectal Cancer and is a patient advocate, representing patients at the National Cancer Institute (NCI) Clinical Trials Advisory Committee and at the NCI Board of Scientific Counselors.
†Peter Kapitein serves as President and Patient Advocate at Inspire2Live and is Ambassador for Alpe d'HuZes, a Dutch cancer research fund-raising organization.