MAYO CLINIC

Acceptability of Electronic Visits for Return of Research Results in the Mayo Clinic Biobank

Janet E. Olson, PhD; Euijung Ryu, PhD; Kelly J. Lyke, BA; Suzette J. Bielinski, PhD; Erin M. Winkler, MS, CGC; Matthew A. Hathcock, MS; Joshua T. Bublitz, BS; Paul Y. Takahashi, MD; and James R. Cerhan, MD, PhD

Abstract

Objective: To understand patient characteristics related to acceptability of returning individual research results via various modalities, focusing on electronic visits (e-visits).

Patients and Methods: Twelve hundred participants from the Mayo Clinic Biobank were selected using a stratified random sampling approach based on sex, age, and education level. Mailed surveys ascertained return of results preferences for 2 disease vignettes (cystic fibrosis and hereditary breast cancer) and a pharmacogenomics vignette. The study was conducted from October 1, 2013, through March 31, 2014.

Results: In all, 685 patients (57%) responded, and 60% reported liking e-visits, although the option of receiving results in an office visit was liked most frequently. Multivariable logistic models showed that the odds of liking the use of e-visits for returning results for cystic fibrosis and hereditary breast cancer were higher among those with higher education and better genetic knowledge and among those not living in proximity to the Mayo Clinic (Rochester, Minnesota). Level of genetic knowledge was not considerably associated with accepting e-visits, whereas education level remained important. For all vignettes, those who are divorced were less likely to accept e-visits.

Conclusion: Researchers are faced with a difficult challenge of returning results with a method that is both acceptable to recipients and logistically feasible. This study implies that the use of e-visits may be a viable option for return of results to stratify the chasm between in-person genetic counseling and online portal receipt of results.

 ■ Mayo Clin Proc Inn Qual Out 2018;2(4):352-358

From the Department of Health Sciences Research, Division of Epidemiology (J.E.O., K.J.L., S.J.B., J.R.C.), Department of Health Sciences Research, Division of Biomedical Statistics and Informatics (E.R., M.A.H., J.T.B.), Center for Individualized Medicine (E.M.W.), and Department of Medicine, Division of Primary Care Internal Medicine (P.Y.T.), Rochester, MN.

Many biobanks have painstakingly collected DNA on thousands of participants,[1-5] and with the rapidly decreasing costs associated with large-scale genotyping and sequencing, many of these biobanks have, or will likely soon have, genetic data on many thousands of individuals.[6-8] Recent studies have consistently found that many participants are interested in receiving, and perhaps expecting to receive, their individual genetic research results from studies in which they enroll.[2,9-12] One of the major challenges to biobanks is how to return these results to participants in a way that is acceptable to participants and logistically feasible by the biobank. However, there are few reports on the current participant preferences for methods by which they receive individual research results. Wright et al[13] reported that participants approved of their planned methods of returning results scheduling by phone, followed by a face-to-face meeting and a written report. However, they were not presented with other options of receiving results, and, as they reported, there are no established models for giving or receiving multiple genomic-based research results related to various medical conditions as is typically received in thousands of patients with whole-exome/genome sequencing. The traditional method of return of results by a face-to-face meeting with a genetic counselor or other clinical genetic professional is not practical in the setting of multiple results per person for perhaps thousands of participants, especially those not presenting symptoms. In-person clinical appointments, the current standard approach for return of individual genetic research results, is not a scalable method for return of research results in large

Mayo Clin Proc Inn Qual Out ■ December 2018;2(4):352-358 ■ https://doi.org/10.1016/j.mayocpiqo.2018.07.004
www.mcpiqojournal.org ■

biobanks. Sukenik-Halevy et al[14] found that the average time for in-person counseling and patient follow-up ranges from approximately 2 to 4 hours. Therefore, for large biobanks, in-person counseling is not feasible and alternative strategies need to be developed. Murphy Bollinger et al[15] presented various choices to 1500 potential biobank participants and found that people were more interested in obtaining a detailed report than having access to someone who would explain the results. However, results among potential participants vs those already enrolled may differ. Thus, we conducted a survey of participants in an existing biobank to query their receptivity for various possible methods of return of results, including use of electronic visits (e-visits, defined as the electronic provision of a written document of genetic test results along with management recommendations). Furthermore, we examined whether acceptability of e-visits is associated with certain patient characteristics, including their underlying level of genetic knowledge.

PATIENTS AND METHODS

Participants (n=1200) were selected from patients enrolled in the Mayo Clinic Biobank.[5] Briefly, the Biobank includes Mayo Clinic patients older than 18 years who were able to provide informed consent. Patients were asked to complete a baseline health history questionnaire, provide a blood sample, and allow access to medical record data.[5] At the time of this study, approximately 35,000 persons had enrolled.

Participants were stratified by age group (18-30, 31-40, 41-50, 51-60, 61-70, and 71+ years), education (high school or less vs at least some college), and sex. Fifty patients were randomly selected from each of the resulting 24 groups, except for the subgroup of "Males, 18-30 years." Only 40 males in that age group had an education of "High School or less." Therefore, all participants were selected from this group, and 60 were selected from the group of "Males, 18-30 years, at least some college."

The survey instrument was 7 pages long and included questions assessing return of results preferences to specific vignettes, including cystic fibrosis, hereditary breast and ovarian cancer syndrome, and pharmacogenomics. Cystic fibrosis was chosen because it is a recessive disorder that was hypothesized to be of greatest interest to those still in their childbearing years. Hereditary breast and ovarian cancer syndrome was selected because of its dominant inheritance pattern and was hypothesized to be of interest to participants in all age groups. Pharmacogenomics was included because of its broad general appeal and because a new pharmacogenomics project was being planned at the time. Patients were first asked whether they would want to receive results of that type and whether they liked or disliked receiving results by various possible methods (office visit, genetic counselor, and e-visits). For the pharmacogenomics scenario, a pharmacist visit was substituted for the genetic counselor visit, and it also offered an option of receiving results via the Mayo Clinic Online Patient Portal. Overall level of genetic knowledge was assessed by adding the number of correct answers from 7 general genetics questions. The survey was deliberately kept brief to increase response rates and generalizability (see Supplemental Material, available online at http://mcpiqojournal.org/).

All 1200 participants were mailed an invitation packet that included a cover letter, questionnaire, and return envelope. If no response was received within 30 days, a second identical packet was mailed (n=680). Recruitment was closed after an additional 30 days. All numeric data were verified by double data entry of all numeric data fields.

This protocol and all patient contact materials were approved by the Mayo Clinic Institutional Review Board.

Basic characteristics of patients who responded to the survey and their survey responses were summarized using percentages for all categorical variables. Participants were asked to express the level of acceptability for each option for receiving individual research results using a 4-point scale (dislike it very much, dislike it somewhat, like it somewhat, and like it very much) and were combined into 2 categories: like (like it very much and like it somewhat) and dislike (dislike it very much and dislike it somewhat). The main focus was their level of acceptance of e-visits. Association between acceptance of e-visits and each basic demographic characteristic and the level of genetic knowledge were first tested univariately

TABLE 1. Basic Demographic Characteristics of Mayo Clinic Biobank Participants and Their Preferences on e-Visits for Receiving Individual Research Results Across 3 Vignettes

Characteristic	Overall cohort (n=685)	Cystic fibrosis		Hereditary breast/ovarian cancer syndrome		Drug-related gene testing	
		Like, No. (%[a])	*P* value[b]	Like, No. (%[a])	*P* value[b]	Like, No. (%[a])	*P* value[b]
Age (y), No. (%)			.98		.98		.05
<30	68 (9.9)	38 (60.3)		38 (58.5)		42 (64.6)	
31-40	94 (13.7)	52 (63.4)		51 (60.7)		51 (57.9)	
41-50	101 (14.7)	47 (54.0)		47 (51.1)		61 (62.9)	
51-60	136 (19.9)	62 (51.2)		64 (51.2)		77 (59.7)	
61-70	149 (21.8)	67 (55.8)		72 (56.3)		75 (58.1)	
Over 70	137 (20.0)	56 (59.6)		53 (54.1)		43 (41.3)	
Sex, No. (%)			.66		.87		.14
Male	326 (47.6)	152 (56.1)		147 (53.1)		159 (54.6)	
Female	359 (52.4)	170 (57.4)		178 (56.5)		191 (59.5)	
Race, No. (%)			.71		.20		.77
White	656 (95.8)	307 (56.8)		312 (54.8)		338 (57.5)	
Others	29 (4.2)	15 (57.7)		13 (56.5)		12 (50.0)	
Residential location, No. (%)			.12		.30		.39
Olmsted County	263 (38.4)	121 (56.0)		128 (55.4)		133 (54.5)	
Other southeastern Minnesota	152 (22.2)	70 (55.1)		67 (51.9)		73 (54.1)	
Other Minnesota	93 (13.6)	47 (59.5)		48 (60.0)		56 (70.0)	
Other United States	177 (25.8)	84 (57.9)		82 (54.0)		88 (57.5)	
Education, No. (%)			.02		.02		<.001
High school or less	304 (44.4)	117 (48.6)		118 (47.4)		128 (50.0)	
At least some college	381 (55.6)	205 (62.9)		207 (60.4)		222 (62.4)	
Marital status, No. (%)			.01		.10		.12
Married	521 (78.9)	256 (58.9)		251 (56.2)		267 (57.2)	
Divorced	63 (9.6)	20 (41.7)		23 (44.2)		27 (51.9)	
Never been married	76 (11.5)	36 (55.4)		38 (54.3)		40 (56.3)	
Genetic knowledge, No. (%)			.03		.01		.14
All correct (q2_correct)	335 (48.9)	183 (64.2)		178 (61.4)		186 (61.2)	
Some incorrect	350 (51.1)	139 (49.3)		147 (48.7)		164 (53.3)	

[a]Percentages are calculated on the basis of participants who want to receive individual research findings for each vignette (~90% of the overall cohort).
[b]*P* values are for comparing patients who like to receive research results via e-visit for each vignette for each characteristic compared with those who dislike. Rao-Scott χ^2 tests were performed adjusting for the survey sampling schema.

for each vignette, using Rao-Scott χ^2 test, adjusting for the survey sampling weights.[16] Multivariable logistic models were used to identify patient characteristics associated with acceptance of e-visits, simultaneously adjusting for the sampling weights, with variable selection via elastic net approach,[17] which is a penalized regression model that performs well when variables are correlated (eg, education attainment and level of genetic knowledge in this study). The selection of lambda, the shrinkage parameter in the elastic net, was done by repeating 10-fold cross-validation 1000 times. The final multivariable logistic regression models were refitted adjusting for survey sampling weights, using the variables with nonnegligible information from the elastic net approach. Statistical analysis was done in SAS 9.4 (SAS Institute Inc) and R 3.2.3 (R Foundation for Statistical Computing). *P* values of less than .05 were considered statistically significant.

RESULTS

Patient Characteristics

Of the 1200 surveys mailed to selected participants from the Mayo Clinic Biobank, 685 (57%) responded, 25 (2%) refused, and the remainder (490 [43%]) did not respond in the study period. Compared with those who

Mayo Clin Proc Inn Qual Out ■ December 2018;2(4):352-358 ■ https://doi.org/10.1016/j.mayocpiqo.2018.07.004
www.mcpiqojournal.org

TABLE 2. Participant Characteristics Associated With Liking e-Visits for Receiving Individual Research Results in the Mayo Clinic Biobank

Characteristic	Cystic fibrosis		Hereditary breast/ovarian cancer syndrome		Drug-related gene testing	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Age group (y), No. (%)	—	—	—	—		
<30					Reference	
31-40					0.93 (0.72-1.18)	.54
41-50					0.98 (0.77-1.23)	.85
51-60					0.81 (0.65-1.01)	.06
61-70					0.97 (0.78-1.21)	.78
Over 70					0.46 (0.37-0.57)	<.01
Female	—	—	—	—	0.69 (0.65-0.75)	<.01
Residential location, No. (%)						
Olmsted County	Reference		Reference		Reference	
Other Southeast Minnesota	0.96 (0.87-1.05)	.37	0.8 (0.73-0.88)	<.01	1 (0.91-1.1)	.98
Other Minnesota	1.24 (1.11-1.37)	<.01	1.28 (1.15-1.41)	<.01	1.74 (1.57-1.94)	<.01
Other US	1.87 (1.71-2.05)	<.01	1.39 (1.28-1.52)	<.01	1.27 (1.16-1.38)	<.01
Education, No. (%)						
High school or less	Reference		Reference		Reference	
At least some college	1.51 (1.36-1.67)	<.01	1.39 (1.26-1.54)	<.01	2.06 (1.86-2.28)	<.01
Marital status, No. (%)						
Married	Reference		Reference		Reference	
Divorced	0.39 (0.35-0.44)	<.01	0.53 (0.47-0.59)	<.01	0.62 (0.55-0.69)	<.01
Never been married	0.78 (0.67-0.91)	<.01	1.05 (0.91-1.21)	.48	1.13 (0.96-1.32)	.13
Genetic knowledge, No. (%)					—	—
All correct	1.64 (1.52-1.77)	.01	1.69 (1.58-1.81)	<.01		
Some incorrect	Reference		Reference			

Variables having negligible information (estimated through elastic net approach) were marked as "—" and not included in the final multivariable models.

completed the survey, noncompleters were younger (mean age 46 years among noncompleters vs 55 years among completers; $P<.001$), less educated (56% of noncompleters had a high school education or less vs 44% of the completers; $P<.005$), less likely to be white (88% of noncompleters were white vs 96% of completers; $P<.001$), and less likely to be married or in a marriage-like relationship (62% of noncompleters vs 76% among completers; $P<.001$). Approximately 50% of respondents correctly answered all questions related to general genetic knowledge.

Preferred Delivery Mode of Return of Results

The vast majority of survey respondents were consistently interested in receiving their individual research results regardless of disease type (84%, 86%, and 10% for cystic fibrosis, hereditary breast and ovarian cancer syndrome, and pharmacogenomics, respectively). In all vignettes, the option of receiving these results in the setting of an office visit with a genetic counselor was liked most frequently, with approximately 90% of the participants reporting that they would like receiving disease-related results in that manner. For pharmacogenomic results, participants liked the option of office visits with a pharmacist only slightly more frequently than telephone conferences (81.8% vs 81.1%, respectively). E-visits and use of the patient portal (the latter option was presented for pharmacogenomic results only) were equally appealing across the 3 vignettes. Fifty-eight percent of respondents said they would like (somewhat or very much) receiving results via e-visits or via patient online services (for pharmacogenomics). However, among those reporting that they would like receiving results electronically, most only liked it "somewhat" (60% for cystic fibrosis, 63% for hereditary breast and ovarian cancer syndrome, and 74% for pharmacogenomics) as compared with liking it "very much."

Factors Associated With Liking E-Visits

Univariately, the Biobank participants who liked e-visits as a method of receiving genetic results across all 3 vignettes did not vary by age but were considerably more likely to have higher education level and better genetic knowledge (Table 1). Participants who are divorced were less likely to accept e-visits (eg, 59%, 55%, and 42% for liking e-visits for cystic fibrosis for those married, never been married, and divorced, respectively; P=.01). Older participants were less likely to accept e-visits for pharmacogenetics test results (65% vs 41% for liking e-visits among those younger than 30 years and older than 70 years, respectively) but not for cystic fibrosis and hereditary breast and ovarian cancer syndrome.

Multivariable logistic regression models using a variable selection approach via elastic net showed that education level and overall level of genetic knowledge were independently associated with the acceptance of e-visits for receiving research results for cystic fibrosis (odds ratio [OR], 1.51; 95% CI, 1.36-1.67 for some college; OR, 1.64; 95% CI, 1.52-1.77 for better genetic knowledge; Table 2). Similar association results were observed for hereditary breast and ovarian cancer syndrome. For the pharmacogenomics outcome, the level of genetic knowledge was not associated with acceptance of e-visits, whereas higher education level remains important (OR, 2.06; 95% CI, 1.86-2.28; Table 2). In addition, those not living in proximity to the clinic (eg, outside the Mayo Clinic catchment areas) were more likely to accept e-visits for all 3 vignettes (eg, OR, 1.87; 95% CI, 1.71-2.05 for liking e-visits for cystic fibrosis). However, those older than 70 years were half as likely to accept receiving pharmacogenomics results via e-visit than were those younger than 30 years (OR, 0.46; 95% CI, 0.37-0.57). Participants who were divorced were less likely to accept e-visits for all vignettes (Table 2).

DISCUSSION

The Mayo Clinic Biobank is a general biobank with many ongoing and proposed research projects that are, or will soon, yield vast quantities of individual research results. We therefore surveyed 1200 of our participants to understand their receptivity toward various models for receiving their genetic test results from our ongoing work.

There is a dearth of models for returning genetic data in a way that is more easily scaled to the current high-volume data than the traditional face-to-face discussion with skilled genetically trained clinicians.[13] We asked patients about their interest in receiving results via multiple possible delivery modes. Although interest was highest for the most personalized setting of the face-to-face office visit, the feasibility is low that we, or any biobank, will be able to staff or bear the costs of returning all future results in this manner in the current age of high-volume data. Although not their preferred mode, participants were relatively open to the possibility of receiving results via an e-visit with a genetic counselor, with half of our participants stating that they would like it somewhat or very much. We found that both the highest level of education achieved and the genetic knowledge of our participants independently influenced the likelihood of participants liking e-visits to receive genetic results.

Interestingly, participants' age impacted the acceptance of e-visits to receive genetic results related to medications (pharmacogenomics) but not those related to disease risk. Persons older than 70 years were less likely than younger persons to favor an e-visit to discuss their pharmacogenomic test results. We hypothesize that this is related to the increased prevalence of polypharmacy in this population. A recent study of national US data found that 39% of persons aged 65 years or older had 5 or more prescriptions in the 30 days before the time of the survey.[18] In recent data from our institution of an analysis of 5 important pharmacogenes (*CYP2D6, CYP2C9, CYP2C19, SLCO1B1*5*, and *VKORC1*), we found that nearly everyone (99%) was likely to carry at least one actionable variant in one or more of these genes.[19] Therefore, the probability of a person currently taking a medication affected by pharmacogenomic test result is influenced greatest by the number of medications currently taken. Consequently, our data suggest that future pharmacogenomic studies should consider incorporating a more interactive approach, such as a medication therapy management consultation, rather than e-visits, to return results to older age groups

Mayo Clin Proc Inn Qual Out ■ December 2018;2(4):352-358 ■ https://doi.org/10.1016/j.mayocpiqo.2018.07.004
www.mcpiqojournal.org

(those with the most current prescriptions affected by genetic tests). This older population is most likely covered by Medicare insurance (in the United States), which pays for medication therapy management consultations among those who meet the eligibility criteria. Implicit in this approach is the need to educate pharmacists about pharmacogenomics and its impact on medication management.

E-visits, which were defined in our survey as "a new way to get the opinion of a medical expert…. (in which) genetic tests would be reviewed and management recommendations would be provided," could be thought of as a step between personal interaction with an expert and a simple report on the findings. E-visits build on the growing use of patient portals and electronic communication between physicians and patients that has occurred after the 2014 "Meaningful Use" ruling from the Centers for Medicare & Medicaid Services.[19] Multiple advantages exist for the use of e-visit technologies for return of research results: (1) this technology allows return of "normal" results that do not need additional comments; (2) it allows customization of information so that the physician can tailor results to the patients' interests, returning, for example, only that information that is actionable; (3) it provides patients and physicians with documentation for future reference; and (4) it enhances communication to other members of the care team.

Returning results electronically is not without concern. Otten et al[20] reported that users of telemedicine for online genetic counseling sessions found them to be effective and cost-efficient but were concerned with insufficient verbal communication, despite them being interactive (real-time). Use of e-visits for return of results may suffer from similar problems, especially in more complex cases (ie, patients with clinically important "positive" results) or with patients who are less prepared (ie, older, less "tech-savvy") for use of electronic means to obtain results.

Some limitations of our study should be mentioned. First, although our questionnaire was based on similar questions used in previous studies in similar populations[21] and had a very good response rate in our population, not all the complexities of genetic data could be fully evaluated given limited space available in the survey instrument. For example, we were not able to fully explain the concept of genetic penetrance and that a variant may or may not manifest in a particular person's lifetime. Thus, we do not have a full understanding of our participants' complete knowledge of genetics, nor whether these distinctions would alter their preferences for methods of obtaining their results. Second, our population, although representative of our biobank, cannot be interpreted to represent all patients in our health care system or in other systems. As we reported earlier, our participants are generally better educated than the population in our surrounding communities, with more than 80% having received at least some college education compared with 27% in the surrounding states of Minnesota, Wisconsin, and Iowa.[5]

CONCLUSION

We found that the use of e-visits for return of individual genetic research results was moderately acceptable with participants of the Biobank. Researchers are faced with a difficult challenge of returning results with a method that is both acceptable to recipients and logistically feasible. Future modalities of return of results may require multiple options for participants.

ACKNOWLEDGMENTS

This study was supported by Mayo Clinic Center for Individualized Medicine. The funding source had no role in the study design, collection and analysis of data, or writing of the manuscript.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://mcpiqojournal.org/. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **e-visits** = electronic visits; **OR** = odds ratio

Potential Competing Interests: The authors report no competing interests.

Publication dates: Received for publication April 27, 2018; revisions received July 9, 2018; accepted for publication July 13, 2018.

Correspondence: Address to Janet E. Olson, PhD, Department of Health Sciences Research, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (olsonj@mayo.edu).

REFERENCES

1. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12(3):e1001779.
2. Murphy J, Scott J, Kaufman D, Geller G, LeRoy L, Hudson K. Public expectations for return of results from large-cohort genetic research. *Am J Bioeth*. 2008;8(11):36-43.
3. Gaziano JM, Concato J, Brophy M, et al. Million Veteran Program: a mega-biobank to study genetic influences on health and disease. *J Clin Epidemiol*. 2016;70:214-223.
4. Vanderbilt University Medical Center-Institute for Clinical and Translational Research. BioVU & synthetic derivative. https://victr.vanderbilt.edu/pub/biovu/?sid=194. Accessed June 22, 2017.
5. Olson JE, Ryu E, Johnson KJ, et al. The Mayo Clinic Biobank: a building block for individualized medicine. *Mayo Clin Proc*. 2013;88(9):952-962.
6. Business Wire. Illumina signs multiple biobank deals. http://www.businesswire.com/news/home/20160201005047/en/Illumina-Signs-Multiple-Biobank-Deals. Accessed June 19, 2017.
7. Kvale MN, Hesselson S, Hoffmann TJ, et al. Genotyping informatics and quality control for 100,000 subjects in the Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort. *Genetics*. 2015;200(4):1051-1060.
8. Henderson GE, Cadigan RJ, Edwards TP, et al. Characterizing biobank organizations in the U.S.: results from a national survey. *Genome Med*. 2013;5(1):3.
9. Godard B, Marshall J, Laberge C. Community engagement in genetic research: results of the first public consultation for the Quebec CARTaGENE project. *Community Genet*. 2007;10(3):147-158.
10. Bollinger JM, Scott J, Dvoskin R, Kaufman D. Public preferences regarding the return of individual genetic research results: findings from a qualitative focus group study. *Genet Med*. 2012;14(4):451-457.
11. Meulenkamp TM, Gevers SK, Bovenberg JA, Koppelman GH, van Hylckama Vlieg A, Smets EM. Communication of biobanks' research results: what do (potential) participants want? *Am J Med Genet A*. 2010;152A(10):2482-2492.
12. Facio FM, Eidem H, Fisher T, et al. Intentions to receive individual results from whole-genome sequencing among participants in the ClinSeq study. *Eur J Hum Genet*. 2013;21(3):261-265.
13. Wright MF, Lewis KL, Fisher TC, et al. Preferences for results delivery from exome sequencing/genome sequencing. *Genet Med*. 2014;16(6):442-447.
14. Sukenik-Halevy R, Ludman MD, Ben-Shachar S, Raas-Rothschild A. The time-consuming demands of the practice of medical genetics in the era of advanced genomic testing. *Genet Med*. 2016;18(4):372-377.
15. Murphy Bollinger J, Bridges JF, Mohamed A, Kaufman D. Public preferences for the return of research results in genetic research: a conjoint analysis. *Genet Med*. 2014;16(12):932-939.
16. Rao JNK, Scott AJ. The analysis of categorical data from complex sample surveys: chi-squared tests for goodness of fit and independence in two-way tables. *J Am Stat Assoc*. 1981;76(374):221-230.
17. Tibshirani R. Regression shrinkage and selection via the lasso. *J Royal Stat Soc Series B (Methodological)*. 1996;58(1):267-288.
18. Kantor ED, Rehm CD, Haas JS, Chan AT, Giovannucci EL. Trends in prescription drug use among adults in the United States from 1999-2012. *JAMA*. 2015;314(17):1818-1831.
19. HIMSS. Using patient portals to achieve meaningful use (EP edition). http://www.himss.org/using-patient-portals-achieve-meaningful-use-ep-edition. Accessed March 28, 2018.
20. Otten E, Birnie E, Ranchor AV, van Langen IM. Online genetic counseling from the providers' perspective: counselors' evaluations and a time and cost analysis. *Eur J Hum Genet*. 2016;24(9):1255-1261.
21. Radecki Breitkopf CR, Petersen GM, Wolf SM, et al. Preferences regarding return of genomic results to relatives of research participants, including after participant death: empirical results from a cancer biobank. *J Law Med Ethics*. 2015;43(3):464-475.