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Counseling following direct to consumer genetic testing for Alzheimer's disease

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COUNSELING FOLLOWING DIRECT TO CONSUMER GENETIC TESTING FOR ALZHEIMER'S DISEASE

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MELISSA THOMAS

ABSTRACT

Direct to consumer (DTC) personal genetic testing (PGT) is a popular choice for individuals in the United States who are interested in learning more about their genetic health risks without formally seeing a medical professional. The company 23andMe offers FDA-approved genetic risk tests for conditions including late-onset Alzheimer's Disease (AD), Parkinson Disease, Celiac Disease, and the BRCA1/2 mutations. Although this company's genetic risk testing results are accompanied by a generic information sheet regarding what each individual's result means for each condition, formal genetic counseling is not included in the service. However, when a condition such as late-onset AD has both known genetic and behavioral risk factors, counseling becomes essential in preventing or delaying disease onset. Following a Mediterranean-style diet, regularly exercising, and regularly participating in cognitive activities (e.g. reading the newspaper or playing a musical instrument) are each thought to be protective against developing late-onset AD. Previous studies have shown that customers do not usually make significant lifestyle modifications after completing DTC PGT, though the majority of this literature may not be relevant to late-onset AD as it included customers of DTC PGT companies that no longer exist today and the genetic risk test for late-onset AD at that time was not yet approved by the Food and Drug Administration.

The proposed study is an interventional study that will compare DTC PGT customer exercise, diet, and cognitive activity habits before and after a personalized genetics counseling session. Exercise will be measured using the Godin-Leisure Time Exercise Questionnaire. Diet will be evaluated by a validated food frequency questionnaire evaluating daily servings of fruits, vegetables, and unprocessed nuts. Cognitive activity at the time of survey will be evaluated by a questionnaire asking for the frequency of various cognitive activities, such as reading newspapers, reading books, artistic activities, and social activities.

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LIST OF ABBREVIATIONS

AD.....Alzheimer's Disease

APOE.....Apolipoprotein E

DTC.....Direct To Consumer

FDA.....Food and Drug Administration

GAO.....Government Accountability Office

MET.....Metabolic Equivalent

PGT.....Personal Genetic Testing

SNP.....Single Nucleotide Polymorphism

SRH.....Self-Reported Health

INTRODUCTION

Background

Since entering the mainstream market in 2006, direct to consumer (DTC) personal genetic testing (PGT) has evolved into an industry that offers genetic risk tests for over 10 conditions including Parkinson Disease, BRCA1/BRCA2 mutations, and late-onset Alzheimer Disease (AD).[1] The Food and Drug Administration (FDA) currently classifies DTC genetic tests as medical devices and regulates those that have moderate to high risk of medical implications, such as those that test for specific disease risk.[2] The agency generally does not review DTC tests with low medical risk, such as genetic predispositions towards specific muscle compositions or eye colors.[2] As of 2018 the FDA has only approved one DTC PGT company, 23andMe, to provide disease-specific testing services.[2]

AD is a progressive neurodegenerative disease, and is the most common cause of dementia.[3] The Alzheimer's Association estimated that 5.7 million Americans lived with Alzheimer's dementia in 2018.[3] While there is an early-onset variation of the disease, the majority of Americans acquire late-onset AD.[4] The cause of early-onset AD is well established as a single-gene mutation that can occur on one of three chromosomes, however, the causes of late-onset AD are not yet completely understood.[4] A variant in the apolipoprotein E (APOE) gene is the only genetic risk factor that has been identified for developing late-onset AD.[4] Testing for this variant is offered by 23andMe as part of their "Health and Ancestry" package.[5] Along with genetic risk, it is thought that environmental and lifestyle factors also contribute to an individual's composite risk of developing late-

onset AD.[4] A counseling session with a genetics counselor or other medical professional may promote modification of these additional factors to optimize disease risk reduction.

DTC genetic tests for health risk assessments are not considered standard of care and, thus, there is no required medical intermediary to assist with customer counseling.[6] Although the appealing aspects of personalized medicine and patient autonomy draw many customers to DTC testing, it needs to be balanced with patient safety.[7] While some DTC PGT customers elect to independently discuss their results with healthcare professionals, including genetics counselors and primary care providers, others believe that individuals should have the option to learn about their genetics without intervention by a medical professional.[8]

Along with a desire to learn more about their genetic risks, DTC PGT customers report that one of their top motivations to pursue testing is to improve their health.[9] Despite this intention, several studies have observed that DTC genetic testing customers do not make any significant lifestyle modifications after receiving their results.[10–12] Others have shown only small behavioral changes after completing DTC PGT.[13–15] It remains unclear whether those customers who do seek out counseling from healthcare professionals make more significant changes than those customers who do not.

Statement of the problem

Although various studies have been performed prior to 2017 on lifestyle modifications in customers after completing DTC PGT, the DTC market is continuously changing and, thus, it is an area of research that deserves further attention.[10–15] The genetic test for late-onset AD offered by 23andMe is FDA-approved. This may have a

greater impact on patients than those results from DTC testing offered in the past, which were not approved by any government agency.[6] A high genetic risk result for developing late-onset AD is a life changing piece of knowledge for consumers and a formal counseling session may assist with the implementation of healthy behavioral changes. The symptoms of late-onset AD have been shown to be less severe with an integrated intervention including a combined diet, exercise, and cognitive training program prior to the onset of dementia.[16] Although 23andMe provides a list of local genetic counselors to its customers along with their disease risk results, the service does not include genetic counseling.[17] While their service also provides a detailed guideline for how to interpret results and how to follow up with a medical professional, an included counseling session may be beneficial for patients.[5]

Hypothesis

Individuals who have completed DTC genetic testing for AD will make significant lifestyle changes after meeting with a genetics counselor to discuss their genetic risk results.

Objective and specific aims

As consumers continue to value personalized medicine and patient autonomy, DTC PGT will remain an appealing option for many individuals. This study will evaluate the potential benefits of receiving post-PGT counseling from a healthcare professional regarding patient risk for late-onset AD. The study's specific aims are to:

1. Compare differences in dietary habits before and after receiving PGT counseling.

2. Compare differences in exercise habits before and after receiving PGT counseling.
3. Compare differences in cognitive and intellectual activities before and after receiving PGT counseling.

REVIEW OF THE LITERATURE

Overview

Direct to Consumer Genetic Testing

Direct to consumer (DTC) genetic testing services provide customers with genetic analyses belonging to one of three subgroups: identity-seeking testing (ancestry or ethnicity testing); disease risk testing; and curiosity driven testing for specific physical characteristics, such as earlobe type and muscle composition.[18] Customers ship a company providing testing services a sample of their DNA, typically saliva or a swab from the inside of the cheek, and avoid the process of scheduling an office visit to see a medical professional. Thus, DTC genetic testing is an appealing option for individuals who do not regularly see a healthcare provider or who have poor access to primary care providers or genetic specialists. Customer DNA is then analyzed for single nucleotide polymorphisms (SNPs), variants of single base pairs in a DNA sequence.[19] For example, a SNP in the apolipoprotein E (APOE) gene is associated with increased risk for developing late-onset Alzheimer Disease (AD).[5]

While DTC genetic testing is offered for multiple reasons, including learning more about ancestry or one's genetics for certain traits or characteristics, the most controversial aspect is testing for disease-risk.[18] When it was introduced, this product was new regulatory territory for the United States Food and Drug Administration (FDA). Some companies providing DTC genetic tests reported that their analyses were not intended to be diagnostic and, thus, should not be subject to regulation by the FDA.[1] However, the scientific and medical communities argued that customer interpretation of

results could have clinical implications and that the validity of these tests should be confirmed and monitored by a government agency.[1] In 2010, these disputes led to a Government Accountability Office (GAO) report, as well as a congressional hearing on the subject of DTC genetic tests.[1] The GAO report concluded that the DTC industry was offering misleading and impractical disease risk testing.[1] While the congressional hearing highlighted the need for consistent, accurate DTC personal genetic testing (PGT), no decisions regarding regulation were made at that time.[1] In 2012, the FDA determined that DTC genetic testing met the requirements of a device and required 23 DTC genetic testing companies to remove health-related interpretations from their offerings until they were approved the FDA.[1] As a result of the new regulations, many companies stopped offering DTC tests. For example, Navigenics, one of the larger DTC genetic testing companies at the time, was sold and put an end to their health-related testing.[20]

While the FDA's 2012 decision could have permanently ended DTC disease risk testing, the DTC industry was optimistic in their future PGT role given continued public interest in genetics and precision medicine. Prior to the 2012 FDA regulations, these genetic tests were already in high demand - the number of companies offering DTC genetic testing for health-related conditions essentially doubled from 14 in 2002 to over 30 in May 2010.[21] In 2010, DTC PGT companies offered tests related to more than 50 conditions.[21] Consumer interest in these tests continued to grow and according to a 2016 review of the industry, by January 2016 there were 246 companies offering some variation of web-based genetic testing.[22] However, because of the 2012 FDA regulations, many of these companies could not offer diagnostic health-related information and

instead offered raw genetic testing results.[22] In 2015, the web-based genetic testing service 23andMe adapted their testing to meet the new FDA regulations implemented after the agency's decision to increase DTC genetic testing oversight.[13] In April 2017, the government agency approved 23andMe to provide testing for 10 additional diseases and conditions, including Parkinson's disease, late onset Alzheimer's disease, and Celiac disease.[6] In November of that year, the FDA announced that genetic carrier screening tests were to be exempted from premarket review and would only be held to a one-time review by the FDA prior to entering the market without further view.[23] This decision made the process for FDA approval of DTC testing significantly more streamlined and efficient. Most recently, in March 2018 the FDA approved 23andMe to provide information on 3 genetic variants of the BRCA-1 and BRCA-2 genes.[24]

The demand for DTC genetic testing will continue to rise. According to a recent Kalorama Information report, the DTC genetic testing market was valued at around $99 million in 2017 with a projected growth of up to $310 million by 2022.[25] Contributing to this market growth was the 2018 announcement that the biotechnology company Perkin-Elmer will begin to offer genetic testing for 34 conditions as a collaboration with the DTC sequencing group Helix.[17] This projected growth, along with the 2017 FDA announcement introducing a more flexible approach to regulating health-related DTC genetic testing, suggests that personal genetic testing will continue to have a role in the future of health care and patient education as long as the services are affordable.[23] With advances in genome sequencing technology, such as high-throughput sequencing, generating the an individual's sequence of SNPs has become much faster and less cost

prohibitive.[26] The cost for the health and ancestry report offered by 23andMe was $199 in 2018, much lower than the original price of $999 in 2007.[9]

Many DTC genetic testing companies only provide customers with their raw genetic data because they have not been approved by the FDA to offer diagnostic genetic tests.[19] These companies typically provide customers with all of the SNPs found in their genotyping data, including those that are usually classified as only incidental or secondary findings in formal genetic testing.[19] Individuals can then obtain health-related information from the raw genetic data by purchasing analysis through third-party companies, which provide more information on those genetic variants that may influence a customer's medical decisions.[19] In this third-party arrangement, the DTC company providing genetic information avoids making any health-related diagnoses or recommendations and typically provides a disclaimer that the information provided is not verified for medical use.[19] Some consider this to be a loophole around FDA regulations on DTC genetic testing.[27] Additionally, the accuracy of these third-party interpretations has recently been called into question. A 2017 study by Tandy-Connor et al. showed that a group of these third-party companies base their reports on publicly accessible genetic databases, which may have incorrect risk classifications.[19] In general, the companies attempt to avoid inaccurate results by reporting on individual genetic variants, which reduces the use of extensive, and potentially invalidated, algorithms that simultaneously evaluate multiple variants for genetic risk.[27]

While DTC PGT is now a regulated and FDA-approved option for patients interested in learning more about their genetic disease risks, the role of medical providers

and the level of medical guidance that should be required with DTC genetic testing remains controversial. Because DTC genetic tests are not considered standard of care, there is no required medical intermediary to assist with customer counseling after receiving DTC test results.[6] Because each individual's baseline knowledge of genetics and expectations for emotional or medical support differs, it is unclear if there should be an absolute requirement for DTC PGT companies to include counseling in their services.[21] While some consumers feel that they should share their results with either their primary care provider or a genetics counselor, many Americans do not have financial or physical access to a genetics counselor and not all primary care providers feel comfortable interpreting the results of these DTC genetic tests.[6] A 2013 study revealed that only 10% of physicians surveyed by the American Medical Association felt adequately prepared to implement genetics into their practice.[28] Additionally, there are currently only about 4,600 genetics counselors in the United States, or about 1.4 genetics counselors for every 100,000 individuals.[29,30] Most genetics counselors are concentrated in large cities with some states having only two or fewer of these professioanls.[21] Additionally, there are an estimated two to three jobs available for every graduate of a genetics counselor training program.[17] An additional barrier to genetic counseling for some individuals completing DTC genetic testing is the out-of-pocket fee for a genetics consultation.[17] Of note, 23andMe provides a list of genetics counselors in the customer's area as part of their health report to facilitate a more seamless transition from the company to a healthcare professional, if needed.[17] They do not, however, provide any sort of genetics counseling consultation as part of their health-related testing package.[17]

Genetics counselors also face challenges in the setting of providing counseling for DTC testing results. The services offered by DTC genetic companies are often composed of different analyses than those that would be provided by a genetics counselor.[6] Also, when customers receive an entire risk profile based on their genetics, they may overwhelm a genetics counselor with concerns and questions that require more time to review than the allotted time for a typical general genetics consultation.[21] Despite these challenges, the National Society of Genetic Counselors advocates for genetic counselors to be involved in the care of patients who have pursued DTC genetic testing and supports the right of individuals to pursue this testing if it is a well-informed and autonomous choice.[6] The role of genetics counselors in addressing patient misconceptions about the validity and utility of testing, as well as providing patient reassurance, must continue to develop along with the DTC genetic testing market.[6]

Genetics counselors and other medical professionals may also face difficulty when analyzing results with their patients because of the limitations of DTC genetic testing.[19] Many SNP variants reported by DTC genetic testing companies are not absolutely causal of conditions because there are additional underlying risk factors that contribute to disease risk, such as an individual's environment and lifestyle choices.[19] Patients may not understand the impact of these environmental factors when initially reviewing their results.[19] Another limitation of DTC reports is that they may not include testing for all genes that are known to be associated with a specific condition. For example, the genetic health risk report offered by 23andMe provides the consumer's data for just two variants of two genes (LRRK2, GBA) linked to Parkinson disease, while

there are other known pathogenic variants of those two genes, as well as other genes clinically linked with Parkinson disease (PARK2, PARKIN).[31]

Other concerns have been raised about DTC genetic testing services, including an increase in patient anxiety and distress after receiving results that are not delivered in person and the possibility that consumers may not accurately interpret the results.[32] For example, if a customer receives a negative result for the BRCA1/BRCA2 gene, they could incorrectly assume that they have no risk of developing breast cancer. While a potential benefit of PGT is reduced healthcare costs due to lower rates of preventable diseases, healthcare spending may actually rise as a result of unnecessary screening or diagnostic tests ordered to alleviate patient concerns.[11] Additionally, because DTC PGT typically involves different tests than those offered by genetics counselors, excessive spending may also be used on in-laboratory genetic testing to confirm clinically invalid DTC results.[19] A 2017 study by Tandy-Connor et al. found a 40% false positive rate in genetic variants detected by third-party DTC genetic testing.[19]

The demographics of those who utilize DTC genetic testing to assess health risks is skewed towards wealthy white men and women and, thus, not representative of the wider population.[10] According to a survey of 23andMe customers, most participants reported an annual household income of $100,000 or more.[33] From this same survey, it was found that 80% of participants had majority European ancestry compared to around 5% who had African ancestry.[33] Similar demographics have been identified in other studies of DTC genetic testing customers, although the underlying reason is unclear.[10] The discrepancy in the demographics between DTC genetic testing customers and the

general population may contribute to socio-economic health differences.[7] If, over time, DTC PGT is shown to significantly improve customer health, it may become an ethical concern that only a limited proportion of the United States population has financial access to these services. As the market for DTC genetic testing continues to develop, potential shifts in its consumer demographics will likely be monitored closely.

Although DTC PGT has limitations, this form of genetic testing has largely been supported by the public's interest in precision, genetics-based medicine and patient autonomy.[9,7] Some patients opt for DTC PGT because they prefer a completely remote process in which they can independently review their results without seeing a professional.[34] Most consumers provided the following as their reasons for purchasing DTC genetic health-risk tests: curiosity about their genes; a desire to find out about their disease-related risks; and interest in improving their health.[7] Sites like 23andMe target these reasons when they advertise that their service can identify lifestyle factors that may be associated with the greatest improvements in weight based on an individual's genetics.[5] This potential improvement in health behaviors after utilizing DTC genetic testing may reduce healthcare costs associated with preventable diseases.[9]

Late-onset Alzheimer Disease

Alzheimer Disease (AD) is the most common form of dementia in the United States, with an estimated 5.5 million Americans affected by the late-onset form of the disease and around 200,000 Americans under the age of 65 living with early-onset AD.[3] Approximately two-thirds of Americans with late-onset AD are women.[3] This discrepancy in the sex-specific prevalence of the disease is thought to be related to

women having longer life expectancies.[3] There are also racial differences in the prevalence of late-onset AD, with older African Americans and Hispanics more likely than older Caucasians to have AD or other dementias.[3] These differences are thought to be due to cardiovascular risk factors, including diabetes and hypertension, as opposed to a difference in the prevalence of high-risk genetic variants, suggesting that health behavior interventions may have a greater benefit on these minority populations.[3]

The APOE gene is used to assess genetic risk for developing late-onset AD. The APOE gene is found on chromosome 19 and has three forms – e2, e3, and e4, with e3 being the most common (Table 1).[3] One copy of APOE, an allele, is inherited from each parent. The presence of one copy of the e4 form of APOE increases one's risk of developing late-onset AD three-fold when compared to having two e3 alleles. Those who inherit two copies of e4 have an eight-twelve times higher risk of developing late-onset AD than those with two copies of e3. The e2 allele is the least common form of APOE and is thought to be protective against developing late-onset AD.[3]

Table 1: Estimated proportion of the United States population with the possible e2, e3, and e4 pairs of the Apolipoprotein E (APOE) gene. A.[3]

APOE allele pair	Percentage of U.S. Population
e3/e3	61
e3/e4	23
e3/e/2	11
e4/e4	2
e2/e2	0.5

In addition to genetic risk factors for late-onset AD, researchers believe that an individual's risk for developing the disease is influenced by lifestyle and environment.[4] For example, the 2013 PREDIMED-NAVARRA randomized trial showed that adherence

to a Mediterranean-style diet with an emphasis on fruit, vegetable, and unprocessed nut intake improved global cognitive performance independent of APOE genotype.[35] When educating participants on a Mediterranean-style diet, dieticians recommended cooking with extra-virgin olive oil, as well as consuming one ounce of unprocessed nuts and 6 servings each of fruits and vegetables daily. Additionally, lower Mediterranean-style diet adherence has been associated with progressive AD biomarker abnormalities, such as brain beta-amyloid load, in middle-aged adults.[36] Higher diet adherence was estimated to provide 1.5-3.5 years of protection against those abnormalities.[36] Participating in physical activity has also been associated with a reduced risk of developing AD.[37] Higher levels of intellectual and cognitive activities, including reading newspapers, participating in crafts or social activities, and playing a musical instrument, have also been associated with lower beta-amyloid deposition, specifically in APOE e4 carriers.[38] In the setting of research that has shown environmental and lifestyle factors contributing towards the risk of developing late-onset AD, the National Institute of Health currently recommends against genetic testing for APOE variants in individuals as a diagnostic tool.[4] In a formal clinical setting, APOE variant testing is typically only performed for research purposes.[4]

Synthesis of existing research

There is limited existing research on behavioral changes specifically after completing genetic testing for late-onset Alzheimer Disease (AD). Most relevant data is through DTC testing, not formal laboratory testing, since the National Institute of Health does not recommend using apolipoprotein E (APOE) variant genetic testing as a diagnostic tool

for AD.[4] While some studies regarding DTC PGT included genetic risk testing for late-onset AD, at the time that the studies were completed the available tests were not approved by the Food and Drug Administration (FDA).[10,11,15] They also included customers who had purchased PGT from Navigenics, a company that no longer exists today and tested for variants of the APOC1 gene in their disease risk testing for late-onset AD.[39] The APOC1 gene sits next to APOE on chromosome 19 but is not a perfect predictor of APOE genotype.[39]

A 2010 study by Vernarelli et al. examined the effect of receiving APOE genotype results on dietary supplement use among individuals with first-degree relatives with AD.[40] All participants had intact cognitive function at baseline. Six weeks after completing late-onset AD risk assessment, 16% of the participants (N=272) reported a change in their use of dietary supplements. Those who had at least one copy of the risk-increasing e4 allele were 4.75 times more likely to report a change than those who did not have an e4 copy ($p < 0.0001$).[40] One limitation of the study was that patients did not report the exact quantities or ingredients of the supplements they were taking. Also, because the study only included individuals with a first-degree relative with AD, participant behavior at baseline may have been influenced by this increased risk compared to the general population.[40] This study did not evaluate for health behavior changes in the setting of receiving genetics counseling services after completing DTC PGT.

There have been prior studies on direct to consumer (DTC) personal genetic testing (PGT) and subsequent behavioral modifications, however, none were specific to

late-onset AD testing. While early proponents of DTC genetic testing suggested that its introduction may stimulate patient motivation to make healthier lifestyle interventions, several studies have shown that patient lifestyle behaviors do not necessarily change after completing testing.[10–12] In 2011, Bloss et al. gathered information regarding patient exercise behavior, intake of dietary fat, and test-related anxiety both before and after they received results of DTC PGT. DTC genetic risk testing was completed through Navigenics Health Compass. Of the 3639 patients enrolled, analysis was completed on 2037 individuals who completed follow-up surveys (mean follow-up 5.6 ±2.4 months after testing).[10] Participants received estimated lifetime risk results for 22 conditions, including Graves' disease, rheumatoid arthritis, and atrial fibrillation, with sex-specific calculated risks for breast and prostate cancers. In pre-testing and follow-up surveys, dietary fat intake was measured with the use of the 17-item Block Dietary Fat Screener. This screener asks about the intake frequency, from a minimum of once or less per month to a maximum of 5 or more times a week, of the 17 top sources of fat in the American diet. Exercise was assessed with the Godin Leisure-Time Exercise Questionnaire. In this survey, subjects report the frequency and duration of mild, moderate, and strenuous physical activity in an average week. These values are then weighted by each intensity of activity's estimated metabolic equivalent (MET) (Table 2).[10] A total score of 24 MET hours per week or higher is consistent with an active lifestyle.[10] Situational anxiety surrounding testing was measured with a 20-item subscale of the Spielberger State-Trait anxiety Inventory. At the time of follow-up, there were no significant differences between baseline and follow-up survey results in dietary fat intake, exercise, or anxiety.[10]

Table 2: Qualifying activities for each activity type on Godin Leisure-Time Exercise Questionnaire.[10]

Activity Type	Examples
Strenuous exercise (9 METs; rapid heart beat)	running, jogging, vigorous swimming or bicycling, basketball, soccer, cross country skiing
Moderate exercise (5 METs; not exhausting)	fast walking, tennis, badminton, easy swimming or bicycling, alpine skiing
Mild exercise (3 METs; minimal effort)	easy walking, yoga, fishing, bowling, golf

Of note, a limitation of this study was its high drop-out rate. 44% of individuals who elected to undergo testing in the beginning were lost to follow-up.[10] Although it is a convenient data collection method, it is also easy for participants to ignore. Another possible explanation for this high follow-up failure rate is that subject spouses and family members were also allowed to be enrolled in the study and, therefore, each failure to follow-up was unlikely to be independent.[10] Another limitation of this study is that the population is not representative of the general U.S. population, although it is representative of those who purchase DTC genetic testing. Of those who completed the six month follow-up, 84.2% of the participants were white, 23.6% were employees of Scripps Research Institute, which partly supported the project, and 70.4% of participants reported an annual income greater than or equal to $100,000.[10]

In 2013, Bloss et al. published results from a one year follow-up of the same participants of their 2011 study.[10,11] A web survey was used once again and a total of three email requests within a 6-week time frame were sent to each individual as a reminder to complete the questionnaire. In those that completed the one-year follow-up (N=1325), there were no statistically significant differences between their baseline

behaviors and those one year post-PGT in regards to anxiety, dietary fat intake, or exercise behavior.[11] The 2011 and 2013 Bloss studies found no significant diet or exercise changes at both the six month and one year follow-up periods, suggesting that DTC genetic testing may not motivate behavioral changes. These studies were appropriately powered with the large sample size and used validated tests including the 17-item Block Dietary Fat Screener and the Godin Leisure-Time Exercise Questionnaire. The use of web-based surveys may be a source of self-report bias or selective recall. If this were the case, though,, falsely reported favorable lifestyle modifications after DTC PGT would be expected and more significant diet and exercise changes would have been found. It is also possible that self-reporting bias led to participants overestimating their baseline habits, reducing the ability to detect any significant changes to behavior.

These studies also evaluated the relationship between the magnitude of behavioral changes and an individual's average estimated lifetime risk for conditions included in the genetic screening using linear regression. The hypothesis was that those with high lifetime risk would make more significant positive lifestyle changes. However, very few significant associations were observed between elevated risk for a specific disease and change in behavior post-PGT. Those that were significant were nominally so. Using the Godin Leisure-Time Exercise Questionnaire, exercise scores increased long-term by 0.59 MET hours per week in the population at elevated lifetime risk of developing atrial fibrillation ($p=0.01$) and by 0.50 MET hours per week in the population who received a higher than average risk result for developing atrial fibrillation ($p=0.02$).[11] These are not

clinically significant changes. An increase of 0.50 MET hours only represents about 10 minutes of light intensity exercise.

Together, the 2011 and 2013 Bloss studies found that Navigenics Health Compass customers were unlikely to make lifestyle changes six months or one year after receiving their health-related risks scores.[10,11,20] Of note, Navigencs Health Compass no longer exists today. Today's major DTC genetic testing company, 23andMe, offers health risk-related genetic tests, but not for many of the conditions (including atrial fibrillation) that were included in the Navigenics panel.[5] While the results from these studies may not be directly applicable to today's DTC market, customer reactions may be similar after receiving risk scores for diseases, such as AD, that may be linked to poor diet and exercise habits.[16]

In 2017 Gray et al. studied behavior changes in customers who specifically underwent DTC single-nucleotide polymorphism (SNP)-based cancer risk testing.[12] This longitudinal study analyzed baseline (pre-testing) and 6-month response surveys from 762 customers of 23andMe and Pathway Genomics. The 6 month survey asked participants if they had made changes in their diet, exercise behavior, advanced care planning behavior, or use of vitamins/herbal supplements in response to their PGT results.[41] Of note, none of the customers tested positive for genetic variants that are very strongly associated with a malignant diagnosis, however, a minority of individuals received mildly elevated SNP-based PGT cancer risk estimates –24% of individuals received elevated SNP-based genetic risk for colorectal cancer, 24% for prostate cancer, and 12% for breast cancer.[12] The percentage of individuals who reported making diet or

exercise changes after receiving their SNP-based cancer risk estimates was not significantly different between those with elevated risk estimates and those with average/reduced risk estimates for developing breast, colorectal, or prostate cancers (Table 3).[12] The elevated risk group was also not significantly more likely to make changes in regards to cancer screenings, including mammography for breast cancer, colonoscopy for colorectal cancer, and PSA testing for prostate cancer.[12] Of note, customers over the age of 50 were high users of cancer screening tests at baseline as most screening tests in the United States are recommended in patients 50 years of age and older. Because of this population's high use of screening tests at baseline, this group was less likely to have a significant increase in the use of these measures after genetic cancer risk testing. This is unlikely to affect results of the study population as a whole as only 36% of participants were over the age of 50.[12] One significant finding in this study was that men with an elevated risk of prostate cancer were more likely to change their use of vitamins/herbal supplements more often than men with non-elevated risk of prostate cancer (25.0% vs. 11.6% of patients, p=0.008).[15] However, these results may be due to an alpha error given the high number of comparisons made in this study. A limitation of the Gray et al. 2017 study included a relatively small number of customers with elevated cancer risk scores. Because of this there was limited power to detect small behavioral changes. While the initial baseline survey used by Gray et al. asked participants specifically about their daily consumption of fruits/vegetables and number of days per week they participated in vigorous, moderate, and strengthening exercises, the study does not specify the language used in the 6-month post-PGT survey. Based on the published

study, the follow-up survey only asked participants if they had made any changes to their diet or exercise routines but did not quantify these changes, which may have provided more meaningful results. Also, greater changes in behavior may have been observed if the study included customers who had received positive results for the more highly penetrant genes of breast, colorectal, and prostate cancers.

Table 3: Associations of genetic risk scores with diet and exercise modifications at 6 month follow up.[12]

PGT Cancer Risk	# Patients	% of patients who changed diet	p-value		# Patients	% of patients who changed exercise	p-value
Breast CA							
Not elevated	375	34.7	0.5		375	27.7	0.57
Elevated	44	29.5			44	31.8	
Colorectal CA							
Not elevated	524	30.3	0.73		524	24.0	0.27
Elevated	166	28.9			166	28.3	
Prostate CA							
Not elevated	207	24.2	0.70		207	18.4	0.52
Elevated	64	26.6			64	2.7	

A recurring limitation in studies of DTC genetic testing is the lack of generalizability to the United States population as a whole.[10,12] While the populations in these studies are representative of current DTC consumers, in most cases the baseline characteristics of study participants are not consistent with the national population[10]. In the 2017 study by Gray et al., the baseline participant characteristics were 21% non-white or Hispanic, 60% female, and 56% employed with full-time positions with 43% reporting a household income ≥ $100,000.[12] For example, the 2017 Gray et al. study noted that after comparing patient baseline behavioral survey results with national

recommendations, 43% of participants had reported dietary habits that met CDC dietary guidelines and 35% reported exercise routines that met CDC exercise recommendations.[12] According to a 2017 CDC press release, only 9% of American adults meet recommendations for vegetable intake and 12% meet recommendations for adequate fruit intake.[42] If these studies had included individuals with baseline health habits that are more similar to those of the general American population, significant post-DTC PGT behavioral modifications may have been observed. As the market for DTC genetic testing evolves and the services become accessible to a wider range of individuals, the demographics of those who utilize DTC genetic testing, along with their health modifications, may change.

Some studies have, however, found significant changes in health behaviors after DTC PGT.[13,14] A longitudinal study by Olfson et al. (2016) specifically evaluated changes in smoking behaviors of 23andMe and Pathway Genomics customers after receiving DTC PGT (N=1002).[13] The study participants at baseline included 64 current smokers, 270 former smokers, and 646 never smokers. At the 6-month follow up survey only 13 (1%) of the 916 former and never smokers started smoking, while 14 (22%) of the 64 current smokers at baseline reported quitting.[13] This cessation rate is much higher than that reported by the 2000-2015 National Health Interview Survey, which found that only 7.4% of smokers who made a cessation effort were able to recently quit smoking.[43] Secondary analyses showed that participants who had quit smoking at 6 months did not tend to have significantly higher genetic risk results for lung cancer or heart disease than the other study participants, including those who were smokers and did not quit.[13] Olfson

et al. also showed that current smokers at baseline were more interested in their genetic risk results for lung cancer than former and never smokers (OR = 1.8, $p<0.0001$).[13] Across the various smoking status groups, there was no difference in the level of interest for results regarding risk of developing heart disease.[13] The limitations of this study include a rather homogenous population, including 90% white and 78% college graduates, and a small sample size of smokers at baseline. The demographics of the study may have contributed to the high cessation rate in participants, as smokers with a bachelor's degree or higher smoke cigarettes for about half as many years as those with a high school level of education.[41]

Nielsen et al. used a web-based survey to evaluate fruit, vegetable intake and frequency of various classifications of exercise both before and 6 months after receiving PGT results.[15] The study included 1,002 customers of 23andMe and Pathway Genomics. This study was similar to those completed by Bloss et al., however, Nielsen et al. performed a secondary analysis, stratifying their results by customer baseline self-reported health (SRH). SRH was assessed at baseline using a validated 5-point scale to answer questions about one's general health, including physical activity, diet, mood, and energy levels.[15] Among those individuals with lower baseline SRH scores there were significant increases in all outcomes (Table 4).[15] These increases were modest with little clinical relevance. When the results were not stratified by baseline SRH, there were only significant changes in vegetable intake ($p=0.0003$) and strength exercise ($p=0.0153$).[15] These changes were again modest and likely not clinically relevant with estimated vegetable intake increasing by only 0.11 servings per day and reported frequency of

strength exercise increasing by 0.14 days per week.[15] The survey also asked if diet and exercise changes were specifically motivated by PGT results with 30% of subjects reporting having made a diet change and 26% of subjects reporting having changed their exercise explicitly based on their PGT results.[15] These rather low percentages may indicate that the DTC PGT customers were ready to make lifestyle modifications regardless of completing PGT or not. The authors of this article admitted that given the small magnitude of changes they observed, DTC PGT is likely very limited in its ability to effect change.[15] Similar to others, this study introduced a potential self-reporting bias by using web-based surveys.

Table 4: Behavioral observations of lower baseline SRH individuals 6 months after completing DTC genetic testing.[15]

Behavior	Delta	p-value
Fruit intake (servings/day)	0.11	0.0148
Vegetable intake (servings/day)	0.16	0.0005
Light exercise (days/week)	0.25	0.0263
Vigorous exercise (days/week)	0.23	0.0097
Strength exercise (days/week)	0.19	0.0369

In 2018, Hayashi et al. studied lifestyle interventions, including changes in diet, exercise, alcohol use, and smoking habits after participants received results of personal genetic testing.[14] Of note, in this study the testing was not DTC but rather completed at a heredity clinic at the University of Tokyo Institute of Medical Science. Participants met one-on-one with physicians at the time of study consent and also received about one hour

of counseling from the same physician at the time of their genetic risk result disclosure. Patient behavior was evaluated pre-PGT and 3, 6, and 12 months post-PGT. While Bloss et al. used specific questions, including the Block Dietary Fat Screener and a detailed exercise log in their follow-up questionnaires, the questions used by Hayashi et al. were much more general with the option to provide additional details in a free response section.[10,14] The follow-up questionnaires asked participants if they changed their diet, exercise routine, tobacco use, or alcohol use, but did not quantify these changes.[14] Among the 20 subjects, over 60% changed their lifestyles in favor of disease prevention.[14] There were significant increases between the pre and post-PGT scores for patient awareness of ability to prevent disease with lifestyle changes and understanding of the diseases that they might suffer from in the future (Table 5).[14]

Table 5: Mean scores of perceived levels of health and future disease risk prior to and after PGT.[14] *Scores range on a scale of 0-10.

Survey Question	Mean score pre-PGT*	Mean score post-PGT*	p value
If you become sick in 10 years' time, how well do you think you could control your illness?	5.75	7.1	< 0.01
How well does your lifestyle and life attitude help prevention of the diseases you might get in 10 years' time?	4.75	6.4	< 0.05
How well do you think you understand the disease you might suffer from in the future?	5.65	8.1	< 0.01

Although the 2018 Hayashi et al. study used subjects who sought genetic testing through a medical office instead of a DTC service, the results suggest that combining PGT with a medical professional consultation may be effective at motivating healthy

lifestyle modifications. While physicians provided the counseling in this study, a consultation with a genetics counselor in the United States would likely cover the same topics and have similar effects. Limitations of this study included a small sample size (n=20) that is not generalizable to the U.S. population as all 20 subjects were Asian and live in Japan. Another limitation in this study is that the phrasing of the questionnaire may have led to a greater self-reporting bias than the Bloss et al. 2011, 2013 studies. It would be much easier for a study subject to claim they had made a positive change to their diet than to systematically do so in the 17-item Block Dietary Fat Screener used in the Bloss et al. studies to evaluate dietary changes.[10,11] Although significant changes in positive lifestyle behaviors were found by Hayashi et al., it is unclear if the model they used can be realistically reproduced. While private companies offering health-related genetic testing could reasonably offer online consultations, it is unlikely that they would be able to provide the one hour medical consultation included in the study protocol by Hayashi et al.[14]

Although most studies in this area of research have found that DTC PGT customers do not make clinically significant changes to their diet or exercise routines after completing disease risk testing, there is no existing research on the most recent, FDA-approved DTC testing for late-onset AD. Because there are lifestyle-associated risk factors for developing late-onset AD, a genetics counseling session to address lifestyle modifications after receiving DTC disease risk results would likely be beneficial for DTC PGT customers.

METHODS

Study design

The proposed study will be a before-after interventional study evaluating dietary habits and physical activity of direct to consumer (DTC) personal genetic testing (PGT) customers at baseline prior to receiving PGT results, 2 weeks after receiving results pre-genetic counseling, 4 weeks after receiving results post-genetic counseling, and 6 months after receiving results post-genetic counseling. Ongoing cognitive activity will also be evaluated in the study population at baseline, as well as before and after genetic counseling.

Study population and sampling

The study population will consist of adults who purchased the DTC 23andMe genetic health risk testing service, which includes testing for late-onset Alzheimer Disease (AD). All subjects will be 18 years of age or older. The sample size will need to be approximately 142 individuals to detect a significant difference in physical activity after receiving genetic counseling, calculated in metabolic equivalents (METs) per week. The sample size was calculated based on the results of Bloss et al. (2013) using an alpha of 0.05, estimated power of 80%, an effect size of 5, and a standard deviation of 21.270.[11,44] While the effect size found by Bloss et al. in 2013 was 1.9 metabolic equivalent (MET) hours per week, five was selected for this study as it represents the addition of one hour of moderate exercise, or approximately 2 hours of light exercise, in a week.[10] This sample size will also be adequately powered to detect a significant difference in the number of

daily servings of fruit, vegetables, and unprocessed nuts using an alpha of 0.05, estimated power of 80%, an effect size of 0.5, and standard deviation of 1.1.[15,44]

Intervention

All participants in the study will be offered free-of-charge genetic counseling after receiving the results of their DTC health risk testing. Each genetics counseling session will last approximately 20 minutes and will review each participant's late-onset AD genetic testing results. Lifestyle modification strategies to reduce risk will be reviewed in detail during these sessions. Of note, all individuals, including those who decline genetic counseling, receive an information sheet from 23andMe that includes recommendations regarding diet, heart health, and intellectual activity.[5] Counseling sessions may either be held in person or remotely via Thera-link, a secure, HIPAA-compliant web-based conference system. Participants will be able to choose between these two options based on their location and the feasibility of scheduling an in-person counseling session.

Project variables and measurement tools

Demographics

Participants will complete a demographics survey prior to receiving their genetic results. This survey will gather information on sex (male, female, other), age, income, education level (some high school, high school degree, four-year college degree, post-graduate degree), occupation, and race (White, Black, Hispanic, other).

Physical Activity

The Godin Leisure-Time Exercise Questionnaire, used by Bloss et al. (2011, 2013) will be used to evaluate differences in physical activity between baseline, pre-genetic

counseling, and post-genetic counseling time points. The questionnaire will gather information on the frequency and duration of strenuous, moderate, and mild exercise per week. The frequency of exercise sessions per week within each category of intensity will be multiplied by the average reported duration, weighted by its respective MET (3 METs for light exercise, 5 for moderate exercise, and 9 for strenuous exercise).[10] Then, all intensities will be summed to produce a value expressed in average MET hours per week.[10] In this questionnaire, scores are calculated as a weekly leisure activity score, and may range from 0 to 246. This questionnaire has a test re-test reliability of 0.62.[10]

Diet

Because of the association between following a Mediterranean-style diet and a reduced risk of developing AD, the study's questionnaire regarding diet habits will focus on Mediterranean-style diet recommendations. A food frequency questionnaire utilized by Nielsen et al. will be used to assess average daily servings of fruits, vegetables, and unprocessed nuts, with the following possible frequency responses: None; ≤1; 2; 3; 4; 5; ≥6.[15] The survey will define what constitutes a serving of each of these categories.

Cognitive Activities

Cognitive training behavior will be measured through a questionnaire of patient reported frequency of participating in the following activities: reading newspapers, reading magazines, reading books, playing games, playing musical instruments, artistic activities, craft activities, group activities, social activities, and computer activities. Patients will report how many times they participate in each activity in an average week.[38] The scores for each activity will be added into one total cognitive activity score for each participant.

Recruitment

Recruitment for this study will be modeled after the Impact of Personal Genomics Study, which began recruitment in March of 2012.[45] Participants for the study will be recruited with the assistance of the DTC PGT company 23andMe. Customers who purchase genetic health risk testing and provide informed consent to participate in research will be contacted directly by 23andMe with an email outlining the proposed study and inviting them to participate. As part of the study consent process, subjects will agree to share their genetic risk information with the study team. Each participant will be identified by a unique survey ID that will be linked to their genetic risk information to maintain subject confidentiality.[45] Due to an expected 40% loss to follow-up rate based on past studies, recruiting will end after 250 participants have confirmed that they have completed the genetics counseling session.[10] Prior to that time, patients will be recruited continuously.

Data collection

Data will be collected using Qualtrics, a web-based survey service. Participants will also use this service to provide the study team with the date of their genetic counseling session after completion. Because all participants were able to purchase DTC PGT online, they should have adequate access to web-based surveys.

Data analysis

Percentages of the study population who are male, female, White, Black/African American, Hispanic, and other races will be calculated. Percentages of the highest level of education, including some high school education, high school degree, four-year college degree, and post-graduate degree, will be calculated in the study population.

Average age and income of all participants will be calculated. Exercise, diet, and cognitive activity data from pre- and post-genetic counseling will be analyzed with paired t-tests analyzing the mean change and standard deviation among the survey variables. Patient-reported behavioral baseline data and pre-genetic counseling data will also be compared with paired t-tests to analyze for any changes in behavior that may be due to results provided by 23andMe prior to intervention. For diet, separate analysis by means of the Wilcoxon signed-rank test will be performed on fruit, vegetable, and unprocessed nut intake. Because multiple comparisons will be made regarding diet changes, there is an increased possibility for committing an alpha error in at least one pairwise comparison. The Bonferroni correction method will be used to control for this potential error.[46] The average changes in reported exercise, diet, and cognitive activity in those who complete in-person genetic counseling will be compared with those who complete remote genetic counseling using an unpaired t-test. Also, to evaluate for differences in behavioral change based on genetic risk, exercise, diet, and cognitive activity changes between those with elevated genetic risk for late-onset AD and those with normal genetic risk will be compared using linear regression.

Timeline and resources

Six months prior to initiation of recruitment, study investigators will begin to meet and collaborate with representatives from 23andMe. Ethics, the informed consent process, and de-identifying of patient information will be discussed. Recruitment of genetics counselors who will provide counseling sessions will begin 4 months prior to subject recruitment. This is adequate time to recruit genetics counselors and establish their access

to Thera-link for remote counseling sessions. The Principal Investigator will be a certified genetics counselor and co-investigators will include physicians, physician assistants, and additional genetics counselors. One month prior to recruitment, the study will be submitted to the Boston University Medical Campus Institutional Review Board.

While the average number of new 23andMe genetic health risk customers per month is unknown, patient recruitment will be expected to be completed four to six months after its initiation.[45] Administrative support in the form of four student workers or research assistants will be required to assist in data entry.

Data analysis will be completed one year after initiation of recruitment. At this time, six-month post-genetic counseling data for all participants will have been collected and available for analysis. A statistician will be consulted at this time. A manuscript will be submitted when data analysis is complete.

The study team will apply for funding from the National Institute of Health and the National Human Genome Research Institute to compensate genetics counselors for their services.

Institutional Review Board

The study investigates individual behavior and proposes no significant harm to participants and, thus, under common rule expedited category number seven, will be submitted to the Boston University Medical Campus Institutional Review Board for expedited review.[47]

CONCLUSION

Discussion

This study will evaluate the role of genetics counselors in promoting beneficial lifestyle modifications in direct to consumer (DTC) personal genetic testing (PGT) customers after receiving genetic risk assessment for late-onset Alzheimer Disease (AD). Customer behavior will be assessed at baseline, 2 weeks after receiving DTC genetic testing results pre-counseling, 4 weeks after receiving genetic counseling, and 6 months after receiving genetic counseling. Although DTC genetic risk testing may reveal significant disease risk, genetics counseling sessions or referrals are not currently required to accompany this form of testing. For diseases that can be affected by behavioral factors as well as genetic risk factors, a detailed counseling session may be beneficial for DTC genetic risk testing customers. The study is unique because it will compare behavior of individuals before and after receiving post-DTC genetics counseling, instead of comparing individuals before and after completing DTC testing. The study is designed as such to reduce the bias that would be present between individuals who chose to complete genetic counseling, who likely have more resources and motivation to change their behavior, and those who do not. Also, unlike previous studies, this proposal will provide free genetic counseling, either in-person or remotely, to any participants who are interested. This will remove the financial and accessibility burden of genetics counseling on participants. It has been shown that up to 38% of DTC PGT customers who did not utilize in-person genetic counseling would have done so if it had been made available to them.[1] The study is also unique in that it will analyze cognitive activities.

This study has several limitations. First, using patient reported data from web-based surveys could introduce a potential self-reporting bias. Participants may overestimate healthy changes in their lifestyle choices if they suspect that they are expected to be making these changes. There is also expected to be a degree of recall bias when participants estimate their behaviors in an average week. There will be selection bias as the individuals who agree to the free genetics counseling session are more likely to be motivated to improve their health behaviors than those who decline the genetics counseling service. The individuals who participate in this study are also more likely to be motivated to make behavioral changes than the general population because they chose to purchase DTC disease risk testing, demonstrating an interest in their health. There is also potential that an individual's knowledge of their personal risk for other diseases, including coronary artery disease or certain malignancies, may influence their behavioral changes and therefore influence study results. This would be addressed by further analysis of personal health risk knowledge before genetic testing.

There is also inherent limitation in this study because there is no way to prove that a participant's behavioral changes are directly related to the genetics counseling that they receive. The survey 6 months after counseling will have limitations of its own as fewer subjects are likely to respond to this long-term follow-up. Another limitation of the study is that while genetics counselors receive similar training and will be instructed to review specific recommendations, their discussions with study participants cannot be completely standardized. Additionally, there may be differences observed in the behavioral changes between participants who completed in-person genetics counseling and those who

completed remote counseling. The benefit, however, of adding remote counseling as an option for those who do not have geographic access to a counselor is important for recruitment purposes.

Similar to the existing literature, the participants in this study may not be generalizable to the United States population because wealthy white men and women have been found to purchase DTC PGT more frequently than other demographics.[10,33] However, the study will be representative of the general population who undergoes DTC PGT. Of note, the demographics in this study may be more diverse than in studies in the past because DTC is now more established, widespread, and potentially more affordable for a greater proportion of the population. In past DTC PGT studies, African Americans and Hispanics have been underrepresented. These groups, however, are more likely than Caucasians to have AD or other dementias.[3] The racial differences in the prevalence of AD are thought to be due to cardiovascular risk factors, including diabetes and hypertension, as opposed to a difference in the prevalence of high-risk apolipoprotein E (APOE) gene variants.[3] This suggests that lifestyle changes may have a more beneficial long-term effect for these patients.

A potential obstacle for the study will be acquiring funding to appropriately compensate genetics counselors and the research team, including research assistants and statisticians. There are few obstacles expected to obtain a sample size of 250 individuals, as 23andMe has over 5 million customers, .[17]

Summary

As DTC PGT continues to be an appealing option for many Americans who are interested in their genetic health risks, high-quality patient education and opportunity for follow-up will be crucial for patient safety. 23andMe already provides generalized fact sheets about results for their genetic risk testing but does not provide a personalized genetics counseling session or an automatic referral to a genetics counselor. This study hopes to evaluate the role of genetics counselors in behavior modifications following DTC disease risk testing, specifically for late-onset Alzheimer Disease (AD), a condition which is known to have lifestyle as well as genetic risk factors.[3] This study will evaluate changes in exercise, diet, and cognitive activity that are protective against developing AD before and after receiving genetic counseling.

Public health significance

A potential implication of this study is a change in regulating DTC genetic risk testing. The DTC genetic risk testing industry has evolved from a completely unregulated field to one that was almost ended by the Food and Drug Administration (FDA) in 2012 to an industry in which 23andMe can offer multiple FDA-approved genetic risk tests including one for late-onset (AD).[1,19] The DTC PGT market continues to grow and in 2018 DTC disease risk testing began to be offered by a collaboration between Perkin-Elmer and Helix.[17] However, if this study suggests that genetics counseling improves health behavior in DTC customers, the FDA may decide to make stronger recommendations for DTC customers to seek out genetic counseling services. The FDA will not be able to mandate that individuals receive genetic counseling, but it can publish guidelines for the American public regarding what they should do with their results. Alternatively, they

may make stronger recommendations that individuals seek out genetic testing in a formal, laboratory setting with a healthcare professional instead of pursuing DTC options.

LIST OF JOURNAL ABBREVIATIONS

Am J Clin Nutr	American Journal of Clinical Nutrition
Appl Transl Genomics	Applied & Translational Genomics
BMC Med Ethics	Biomed Central Medical Ethics
BMC Med Genomics	Biomed Central Medical Genomics
BMC Res Notes	Biomed Central Research Notes
Br Med Bull.	British Medical Bulletin
Curr Genet Med Rep	Current Genetic Medicine Reports
Eur J Hum Genet	European Journal of Human Genetics
Genet Med	Genetics in Medicine
Genet Test Mol Biomark	Genetic Testing and Molecular Biomarkers
Genome Med	Genome Medicine
Genomics Inform	Genomics & Informatics
J Clin Oncol	Journal of Clinical Oncology
J Genet Couns	Journal of Genetic Counseling
J Community Genet.	Journal of Community Genetics
J Med Genet	Journal of Medical Genetics
J Neurol Neurosurg Psychiatry	Journal of Neurology, Neurosurgery, and Psychiatry
JAMA	The Journal of the American Medical Association
N Engl J Med	New England Journal of Medicine

Off J Soc Res Nicotine Tob	Official Journal of the Society for Research on Nicotine and Tobacco
Transl Res.	Translational Research
Yale J Biol Med	Yale Journal of Biology and Medicine

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