Communicating Genetic Risk Information for Common Disorders in the Era of Genomic Medicine

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Abstract

Communicating genetic risk information in ways that maximize understanding and promote health is increasingly important given the rapidly expanding availability and capabilities of genomic technologies. A well-developed literature on risk communication in general provides guidance for best practices, including presentation of information in multiple formats, attention to framing effects, use of graphics, sensitivity to the way numbers are presented, parsimony of information, attentiveness to emotions, and interactivity as part of the communication process. Challenges to communicating genetic risk information include deciding how best to tailor it, streamlining the process, deciding what information to disclose, accepting that communications may have limited influence, and understanding the impact of context. Meeting these challenges has great potential for empowering individuals to adopt healthier lifestyles and improve public health, but will require multidisciplinary approaches and collaboration.

INTRODUCTION

Genetic risk communication will rapidly broaden in scope and practice as emerging genomic technologies allow more and more individuals to access information about their own genetic makeup, either through their physicians or outside of the medical system. Although communicating about genetic information is currently the special province of medical geneticists and genetic counselors, the limited number of these professionals is unlikely to satisfy the demand for services as genomic medicine expands (49, 50, 79), particularly for information about common disorders such as diabetes or heart disease. In the future, genetic risk information for common disorders will be interpreted, communicated, and utilized in the context of clinical presentation, medical history, and family history, as well as other known risk factors that take into account the entirety of the patient, making primary care a likely home base for the communication of genetic risk information. However, clinicians of all specialties will need to be well versed in the nuances of this communication. The shift in responsibility for genetic risk communication away from genetics specialists should not be surprising, as there is a natural transition in medicine for practices once limited to specialists to be adopted by generalists. For example, family practitioners and general internists have replaced specialists in the routine care of children and adults with Down's syndrome (25), adults with diabetes, and children with asthma. These types of transitions are sometimes driven by a lack of access to specialists (54).

Although genetic information is unique and identifiable and has implications for blood relatives, genetic risk factors only rarely provide information that is inherently different from that provided by other risk predictors commonly used in health care. The deterministic aspects of most genetic tests are not inherently different from those when early evidence of a medical syndrome is discovered through screening. And the susceptibility aspects of genetic testing are not significantly different from those of common risk factors such as age, blood pressure, smoking status, cholesterol, and family history (34). We also maintain that genetic risk prediction is only rarely qualitatively different from prediction based on other medical risks. A growing body of evidence suggests that the lay public views genetic information about common disorders the same way it views other medical information, and feels it should be treated similarly (28, 91). In rare cases where some types of genetic information could lead to stigmatization or discrimination, it has been suggested that the health care system's precedent for treatment of psychiatric information may be followed (34).

In a 1999 review article titled "Communicating Genetic Risk Information," Marteau (71) speculated that those seeking to communicate genetic risk for common disorders might learn from existing methods of communicating other health information such as diagnoses, treatment, and prediction of illness. In that spirit, we first discuss risk communication in medicine, including some examples of tools to quantify disease risk and how they have been used. Second, we provide a synopsis of best practices in risk communication from the literature on both genetic and nongenetic risk assessment. Third, we address some of the opportunities and challenges specific to genetic risk communication. The goals of this review are to provide insight from empirical work on improving genetic risk communication and to address challenges facing the field in the era of genomic medicine.

THE BASICS OF RISK COMMUNICATION

We are bombarded by numerical probabilities on a daily basis. We might learn that there is a 30% chance of a thunderstorm for the upcoming weekend, or that our favorite football team is twice as likely to win if they play at home than if they play on the road. In a similar manner, health-related

risks are frequently communicated as numerical probabilities: A surgeon might summarize the risk of adverse outcomes from a procedure as 1–2%, and a primary care physician might inform a patient with diabetes that his or her risk of heart attack and stroke is nearly doubled. Furthermore, decisions are (and are expected to be) made based on these numerical risk figures—for example, choosing whether to cancel an outdoor activity owing to the chance of a thunderstorm, or choosing whether to proceed with surgery. It is important to realize that an individual brings a lifetime of experience to how he or she perceives, interprets, understands, or even ignores these figures (36).

There is a tremendous amount of literature about risk communication, ranging from how the general public understands the probabilities associated with weather forecasts (58), general health risks (77), and adverse events during therapy (93) to how to communicate genetic risk information (71). Literature on risk communication is abundant (36), but its diversity poses a challenge to synthesis because the various disciplines do not typically overlap (77). The goal of this section is to review selected examples of risk calculators and risk prediction in medicine, providing precedents and principles for incorporating genetic information into medical care.

Risk Calculators in Medicine

The identification of risk factors for disease is one of the cornerstones of epidemiology. Risk can be assessed from factors that are nonmodifiable, such as genetics and demographics, as well as those that are modifiable, such as environment and lifestyle. Family history, although commonly thought of as a proxy for heritable factors, also has shared environmental components. For example, parents and children are more likely to share risky behaviors, such as cigarette smoking, and to share exposure to a given environment. Historically, family history has been considered an imprecise marker for both genetic and environmental risk; nonetheless, early prediction models utilized family history as a surrogate genetic marker to identify individuals at high risk for a given disease.

The Framingham Heart Study (68) was designed to explore hypertension and cardiovascular disease based on the premise that cardiovascular events could be at least partially attributable to lifestyle, environmental factors, and inheritance (26). Over several decades, this study gradually established many risk factors for cardiovascular disease, including smoking, obesity, physical inactivity, hypertension, and hyperlipidemia. The Framingham risk score (FRS) was devised as a way to combine lifestyle and clinical characteristics into a single quantifiable risk for coronary heart disease events. First validated in men in 1982 and further codified in 1998, the FRS quantifies the likelihood of a coronary heart event over a 10-year period based on smoking status, blood pressure, cholesterol levels, and history of hypertension (42). The score has since been refined to calculate intervals other than 10 years and has been validated in women and other populations (24). The FRS was initially devised to help physicians identify high-risk patients who might benefit from more rigorous preventative strategies or lifestyle changes, but it is now available to the general public through the Internet. Other cardiovascular risk prediction methods utilize features not in the FRS, such as C-reactive protein (Reynolds risk score, developed from the Framingham cohort) and family history of cardiovascular disease (ASSIGN, developed from the Scottish Heart Health Extended Cohort) (85, 105).

After the success of the FRS, similar risk prediction models were developed for other diseases, with the focus shifting from a population-based strategy to personalized medicine, including genetic information. The Gail model, first published in 1989, was developed to help physicians counsel women about the risk of breast cancer (37). This model utilizes demographics, past medical history, and family history data to calculate five-year and lifetime absolute risks of breast cancer. It also estimates a woman's risk compared with the risk of the average women of the same demographics but without the subject's medical or family history. The Gail model considers

first-degree relatives (mother, sisters, and daughters) to be significant. Like the FRS, the Gail model was originally developed as a way for clinicians to identify high-risk women for further screening strategies. The Gail model is now readily accessible to the general public via websites and has been utilized in the assessment of cost-effectiveness strategies for screening methods, such as mammography. The Gail model was developed prior to the discovery of the increased breast cancer risk associated with the *BRCA1* and *BRCA2* genes, but it uses family history as a proxy measure to identify patients with increased genetic susceptibility.

In 2008, the World Health Organization devised a risk calculator for osteoporosis called the Fracture Risk Assessment Tool (FRAX) (61). This calculator was designed to help physicians detect high-risk patients who would benefit from preventative treatment or rigorous screening. Unlike the FRS and the Gail model, this calculator was initially designed for online use. It utilizes demographics, body mass index, medical history (steroid exposure, history of fracture, rheumatoid arthritis), risky habits (smoking, drinking), family history (parental fractured hip), and biomarkers (femoral neck bone mineral density) to calculate the probability of a major osteoporotic or hip fracture over 10 years. FRAX also includes diverse geographic and ethnic options to further personalize the risk.

Risk calculators used in clinical practice have evolved to include diverse data on demographics, ethnicity, medical history, lifestyle factors, environmental exposure, family history, and biomarkers. Although personalized genetic data are not yet commonly utilized in the risk calculators that are employed on a large scale, it is likely that genetic data will soon be incorporated into existing risk calculators to further refine risk estimation as we learn more about genetic risk factors for common disorders and as genetic testing becomes widely accessible to the public.

Risk Prediction in Complex Diseases

Complex polygenic diseases, such as diabetes, inflammatory bowel disease, and rheumatoid arthritis, are notoriously difficult to predict. This is due partially to the influence of many genes and to large and heterogeneous gene-gene and gene-environment interactions (59). Genome-wide association studies are currently the most common way of identifying single-nucleotide polymorphisms (SNPs) related to risk of a particular disease. These studies compare many thousands of SNPs in diseased cases against those of healthy controls to identify SNPs conferring increased or decreased risk. They typically require many thousands of patients for a reliable risk prediction model. Despite advances in the identification of genetic markers for disease risk, however, our fundamental knowledge of genetic contribution to disease risk has much room for improvement. In the best-studied complex polygenic diseases, such as diabetes, macular degeneration, and Crohn's disease, it is estimated that less than 50% of heritability is explained by currently identified SNPs (70).

Risk prediction models often group factors as either nonmodifiable (age, sex, ethnicity, location, and genetics) or modifiable (lifestyle factors such as obesity and physical activity). Biomarkers are often utilized to detect preclinical or subclinical manifestations. These biomarkers are typically common tests (such as the use of blood glucose levels for predicting diabetes) but are sometimes novel (such as the use of serum adiponectin levels for predicting diabetes).

In a 2011 review that identified 46 risk prediction models in type 2 diabetes (13), nearly every model included family history, but only 5 included genetic information in the form of genetic risk scores from SNPs. According to this article, the discriminatory accuracy of models using genetics was only modestly improved compared with those using family history alone. Even in large genome-wide association studies, many SNPs significantly linked to diabetes have modest odds ratios compared with modifiable risk factors such as obesity.

As risk prediction models have evolved, the intended audience has also changed. The original risk prediction models were aimed at physicians to help them identify high-risk patients for preventative strategies or preventative research studies. More recently, these models have been made available to the general public, usually via online risk tools or genetic susceptibility panels that utilize no clinical information. In the near future, clinical, demographic, environmental, and genetic data will likely be combined to offer more precise risk prediction directly to consumers/patients. These methods may be strictly informative or financially motivated through tie-ins with health promotion companies, whereas other models will continue to emphasize screening strategies, prevention efforts, and the modifiability of risk for a given disease.

How Well Do Individuals Understand Risk Information?

Numerical probabilities are challenging to communicate effectively to the lay public and even to trained medical clinicians owing to the wide range of scientific and mathematical expertise and personal experiences that affect risk perception and understanding (95). Therefore, a one-size-fits-all approach is likely to be ineffective. Weather reports are a great example. Meteorologists across the country daily communicate the numerical chance of a weather event in the same format, and studies have demonstrated that the general public frequently misunderstands these reports. For example, the public tends to misconstrue the probability of precipitation, such as an 80% chance of rain today, as being deterministic, referring to the proportion of area that will be rained on or the proportion of time it will actually rain (58). In the same manner, patients often do not take the risk figures presented to them at face value, adopt them as true, or even recall them over time (9, 12, 67, 80). Studies of genetic counseling have demonstrated that patients tend to rely more heavily upon personal experience and personal theories of risk than upon communicated risk figures in interpreting and understanding their own genetic risk information (74). Even after a thorough explanation of risk figures, patients in one multicenter study of cancer genetic counseling did not fully understand their risk of developing cancer, sometimes incorrectly underestimating their risk after counseling (9).

Why is risk information so difficult to understand? The psychological, social, and spiritual aspects of a person's life impact how risk is integrated into the individual's complex network of belief systems and life experiences (98, pp. 208–12). Consider a person who has a family history of Huntington's disease, with this person's mother and five of six maternal aunts and uncles having the disease. This counselee may disregard the counseling that he or she has a 50% risk of having the mutation because his or her real-life experience seems to indicate a much higher risk. This scenario demonstrates two key factors that may influence risk perception: (*a*) a concept known as representativeness, which means that an individual applies what happened in a small sample (often a personal experience) to a larger group, including themselves, and (*b*) the general difficulty in understanding numerical values and probability (101, pp. 125–37). **Table 1** summarizes additional factors that impact risk perception and understanding.

Sometimes the explanation for why people do not understand risk information is simply that the communication was unclear. Risk is commonly communicated as a single-event probability: "With this medication, there is a 30% to 50% risk of a bad side effect." Yet this statement of risk does not specify a reference class. In this situation, the risk communicator may intend for the reference class to be the group of all patients on this medication, but an individual patient may think of his or her day-to-day life as the reference class (i.e., this bad side effect will happen on 30% to 50% of the days). A frequency statement makes the reference class clear: Of 10 patients on this medication, 3 to 5 of them will report experiencing this bad side effect (40). Risk communicators are encouraged to present and frame numerical risks in multiple ways in order to attempt to navigate the complexity associated with understanding risk information.

Table 1   Factors that influence risk perception and understanding (adapted from References 98 and 101)

Factor	Description
Individual factors	
Cognitive/emotional traits	Personality traits such as optimism versus pessimism, risk-taking attitudes, and preference for numerical format of risk figures
Numeracy	The ability to understand numerical values and probability (the numerical equivalent of literacy)
Consequences	The range of consequences related to the risk information; consequences can be positive, negative, life altering, neutral, etc.
Uncertainty and the need to reduce uncertainty	The uncertainty associated with risk figures and the emotional need to reduce this uncertainty
Experiential factors	
A priori beliefs	Initial beliefs about risk level
Availability	Prior experiences, i.e., real-life experiences that are cognitively "available" to the client when the risk is presented
Representativeness	Inferences from a small sample (e.g., a family) to a larger group (e.g., a specific population)
Other factors	
Anchoring	Bias introduced by the first concept or risk figure introduced
Binarization	The tendency to simplify risk information and reorient it toward the possible outcomes rather than the likelihood of those outcomes (i.e., viewing numerical risk in two categories—50/50, present/absent, will/will not happen—regardless of the probability presented)
Complexity	The generally complex nature of risk figures, particularly multiple related risk figures presented together or in sequence

Strategies for Presenting Risk Information

The broader risk communication literature provides several evidence-based strategies for presenting risk information, which are summarized in this section.

Present risk information in multiple formats, but avoid qualitative modifiers. Individuals differ in their preference for the format of numerical risk information, and it is therefore important not to assume that any single technique is best in communicating numerical probability. For example, some people may prefer that risk be presented as a percentage (25%), whereas others may prefer a proportion (25 in 100), a population comparison (25 in 100 compared with 5 in 100 for the general population), or even gambling odds (3 to 1) (51). Thus, experts suggest that risk figures be presented in multiple numerical formats if possible ("there is a 25% chance of *x*, or a 25 in 100 chance of *x*"). Additionally, it is generally best to communicate risk in terms of absolute risk rather than relative risk, as individuals tend to be influenced by relative risk information (36). Many individuals prefer that risk figures be presented in qualitative words, such as high or low, but using terms like these typically allows much greater latitude for interpretation than a quantitative format does (73). When using numbers, risk communicators should strive to ensure that the numbers are presented in a format easily understandable to individuals with low numeric literacy (numeracy) (36).

Be conscious of framing biases, and frame risk in multiple ways. The framing of a risk figure is an important consideration. Equivalent risks can be framed in terms of a positive/gain

or a negative/loss, and differences in framing can lead to differences in risk perception. For example, a study of Swiss physicians and patients regarding perception of the treatment benefit of a hypothetical new drug showed that this perception differed among both doctors and patients who received equivalent risk information in the following formats: survival proportions, mortality proportions, relative mortality reduction, and all three presentations of risk (83). This study highlights two important points: (*a*) Physicians (not just patients) were susceptible to framing bias, and (*b*) presenting information about the drug in terms of absolute mortality risk led to the least biased perceptions of the benefit when a combination of three risk formats was used as the reference.

To attempt to circumvent framing effects, it may help to communicate risk information in both positive and negative ways. For example, a 60% risk of developing a condition also means a 40% risk of not developing the condition, or, out of 100 patients with these risk factors, 60 of them will develop the condition and 40 will not (82).

Use pictures, but choose carefully. Graphics in risk communication not only are widely used but have been shown to improve understanding of risk, particularly for those with lower levels of education and numeracy (38, 100, 107). In general, pictographs with 100 boxes have been found to be the best method for communicating percentages, and they are good at communicating both verbatim information and "the gist" of the information (53). Pictographs directly translate percentages into discrete visual units and better communicate the part-to-whole ratio. They can also help to reduce the influence of anecdotal information on how patients interpret risk information (35). One study of graphics found that patients preferred risk information to be presented via multiple graphics (29); however, this finding may simply be due to a cognitive perception that more graphics means the data are more accurate.

Pictographs can be easily created by making a table of 100 boxes and shading in the boxes corresponding to a particular percentage. Pictograph generators are also available on the Internet for public use (e.g., **http://www.iconarray.com**).

Several companies and research studies in genetic risk communication currently utilize graphics, and it is worth noting and building on the work already done. For example, 23andMe uses pictographs of 100 cartoon people with some shaded to depict percentages (**Figure 1**). The Coriell Personalized Medicine Collaborative has used graphics to communicate relative risk figures, providing estimates of disease prevalence as a reference point (**Figure 2**). In this study, Coriell chose to present risk as relative risk in order to consistently report risk figures across multiple diseases and across genetic and nongenetic factors (96). Coriell also presents competing environmental and lifestyle risks that allow recipients to contextualize genetic risk more appropriately.

Denominators matter! Can you visualize 1,000 people in a room? What about 100,000? Most people, particularly those with low numeracy, have trouble doing so. One study of medical risk communication found that individuals, particularly those with low numeracy, often incorrectly recalled or simply disregarded risk figures with large denominators (greater than 5,000); the authors suggested that ratios with smaller denominators (from 50 to 100) are easier to understand and visualize and therefore are more suitable for communicating risk information to patients (39). Using consistent denominators when comparing risks presented as ratios reduces the need for individuals to perform a mental calculation to compare the magnitudes of those risks (84). Also, individuals with low numeracy frequently neglect the denominator when comparing risk figures and focus only on the numerator (known as denominator neglect). For example, when asked which risk figure is higher, individuals commonly say that that 4:100 is higher than 2:50 (because 4 is greater than 2), although in fact these ratios are equivalent (39).
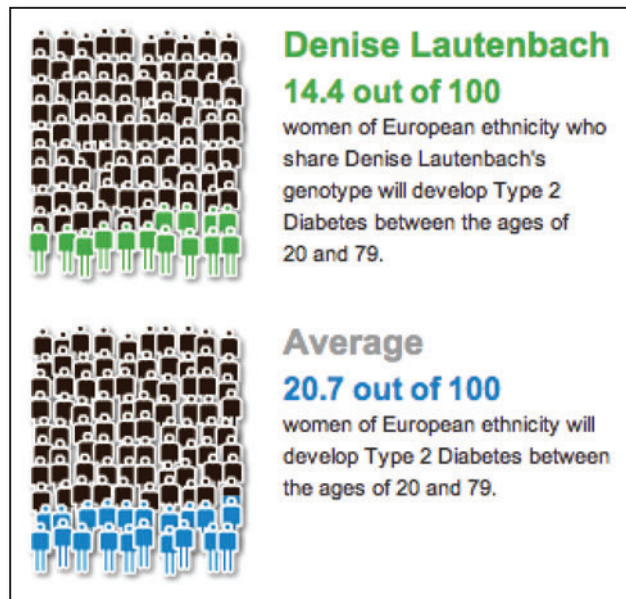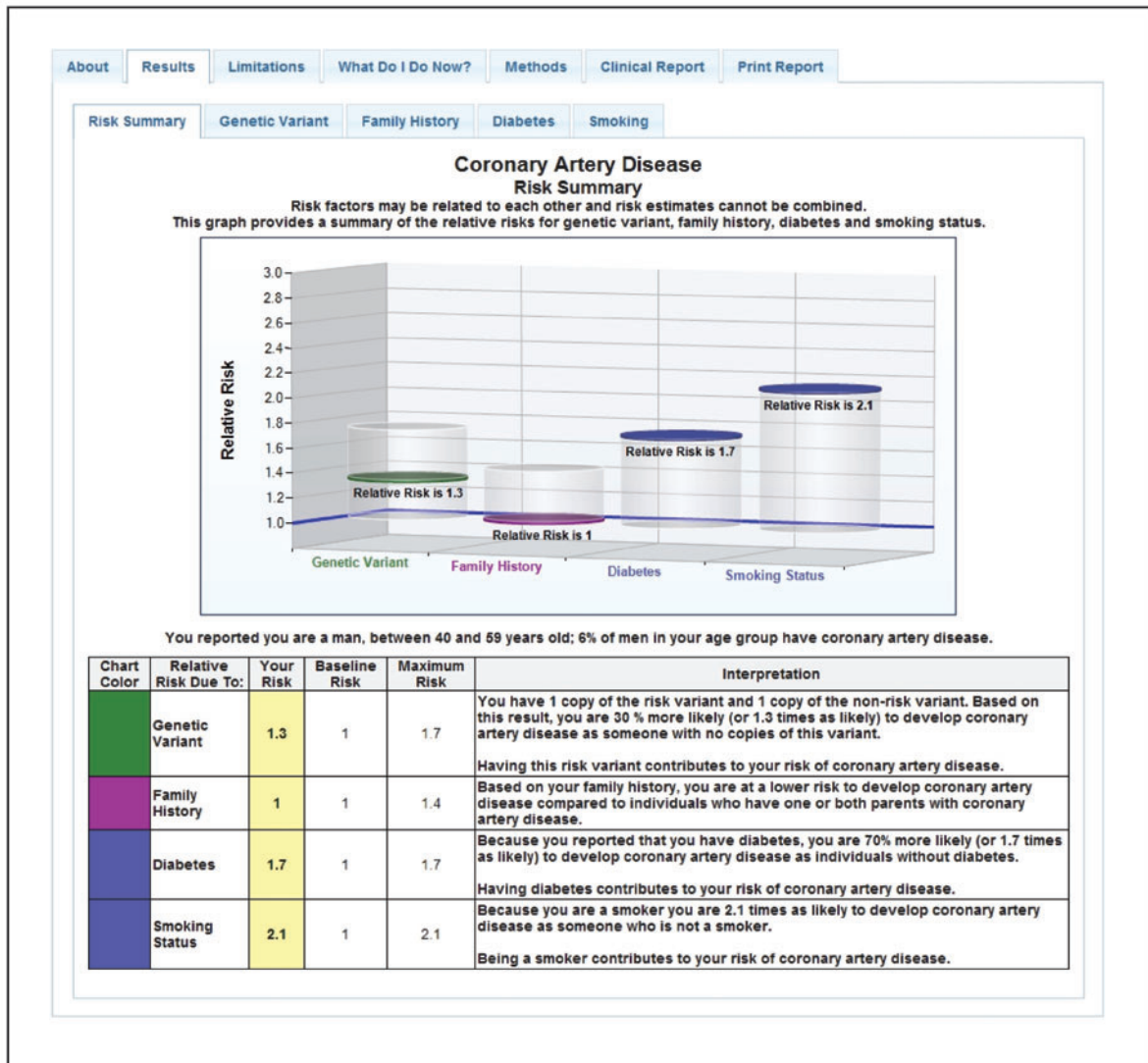
Figure 1

Sample pictographs from 23andMe results. Copyright © 2013 by 23andMe Inc.

Less is more. Experts in risk communication suggest keeping graphics simple and assuming low numeracy to streamline information and emphasize the most important parts of the message (95). High-level statistical concepts, such as confidence intervals, should generally be avoided because people tend to either accept or reject numerical information without cognitively adjusting for its overall quality (84).

Be aware that factual risk information is often distorted by emotions. Using numbers in risk communication gives the impression of a highly rational process, but emotions matter a great deal. Individuals process risk information both cognitively and affectively, and the emotional aspect plays a role in how they understand, adopt, and integrate the risk information and then make decisions based on it. It is important to realize that factual risk information may take second place to "gut feelings," the views of acquaintances, cultural beliefs, past experiences, and a priori perceived risks (95).

Engage recipients in the process. Engagement and interactivity increase both patients' understanding of their disease risk and the likelihood of changing their behavior to reduce their risk (32). Online risk assessment tools offer great potential for the field of risk communication in this regard. These tools can quickly process information on patients' lifestyles, family histories, and genetics to calculate their risk for a given disease using a risk prediction model. They also allow individuals to participate in and interact with the process by inputting their own risk factors (demographics, exposures, habits, etc.) and manipulating results to see how altering certain behaviors might change their risk and potential outcomes. Online risk assessments additionally enhance the relevance of information by allowing messages to be tailored to patients' individual characteristics.

Figure 2

Sample risk summary from the Coriell Institute for Medical Research.

Message tailoring may be helpful in risk communication interventions where behavior change is the desired outcome (60).

Summary. Current models of risk calculation and prediction for common disorders and the evidence-based literature on how to best communicate numerical probabilities provide a framework for communicating genetic risk information. The next section highlights some of the opportunities and challenges associated with genetic risk communication that have emerged through empirical work on the impact of genetic risk assessments for common disorders.

Table 2   Characteristics of the research subjects and randomization in the four Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study trials

		Randomized study arms[a]	
	Subjects	**Comparison**	**Intervention**
REVEAL I (2000–2003)	Cognitively normal adults with a first-degree relative with AD	Genotype nondisclosure (AD risk excluding *APOE*)	Genotype disclosure (AD risk including *APOE*)
REVEAL II (2003–2006)	Same as REVEAL I, but including older adults and targeted recruitment of African Americans	Standard protocol (in-person educational session, extended counseling); genotype disclosure (AD risk including *APOE*)	Condensed protocol (mailed educational brochure, abbreviated counseling); genotype disclosure (AD risk including *APOE*)
REVEAL III (2006–2009)	Cognitively normal adults with or without a family history of AD	Condensed protocol; genotype disclosure (AD risk including *APOE*)	Condensed protocol; genotype disclosure (AD risk including *APOE*, plus *APOE*-associated risk of cardiovascular disease)
		In-person risk disclosure	Telephone risk disclosure
REVEAL IV (2010–2013)	Persons with a diagnosis of mild cognitive impairment	Standard protocol; genotype nondisclosure (AD risk excluding *APOE*)	Standard protocol; genotype disclosure (AD risk including *APOE*)

[a]In REVEAL I, II, and IV, subjects were 1:2 randomized for the comparison:intervention assignment. In REVEAL III, subjects were double randomized (factorial design) to receive either Alzheimer's disease (AD) risk information alone or AD risk plus *APOE*-associated cardiovascular risk information and to receive either in-person risk disclosure or telephone risk disclosure.

CHALLENGES TO COMMUNICATING INFORMATION IN A RAPIDLY EVOLVING FIELD

The rapid pace of genetic discoveries and the evolution of genomic technologies present both opportunities and challenges for the incorporation of genetic risk information into medicine. Since 2000, our research group has studied the behavioral and psychosocial impact (48) of *apolipoprotein E* (*APOE*) genotyping to estimate Alzheimer's disease (AD) susceptibility as part of the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study. *APOE* genotype and AD risk assessment serve as an excellent model for translational trials in disclosing and communicating genomic information because the disease is common (affecting more than 5 million Americans) and because the *APOE ε*4 allele (carried by 20% or more of most populations) is a well-established and robust predictor of AD risk (2, 22). Moreover, the *APOE ε*4 allele is neither necessary nor sufficient to develop AD, making *APOE* a stronger representative of the types of genetic markers that have been identified in the past decade through genome-wide association studies. Although genetic risk assessment is moving quickly away from single-gene, single-disease risk assessment, many of the research questions and challenges addressed in the REVEAL Study are relevant to genetic risk profiling for multiple diseases, and show how it can have myriad effects on emotional well-being, disease beliefs, and health behaviors (88). The following section addresses opportunities and challenges associated with the communication of genetic risk information, using findings from the REVEAL Study as examples. **Table 2** summarizes the research subjects and randomization all four REVEAL Study trials.

Tailoring Communication to Patient Profiles

Numeric risk estimation based on an individual's genetic profile is a cornerstone of personalized genetic medicine. The challenges in creating such estimates are often understated. The validity

of the susceptibility loci used in some models has been questioned (57), and it can be difficult to identify situations where different markers represent the same DNA sequences. Polygenic risk models that attempt to adjust for these factors are limited in number, and these have often not been validated in populations other than Caucasians; thus, the associations between single markers and disease risk are frequently exaggerated (8). Even when genetic risk assessment focuses on a well-established marker for disease, like *APOE* as a marker for AD risk, personalizing risk estimates can be contentious. Questions arise such as whether to adjust for demographic factors (such as sex, race, and education) or environmental factors (18), and inferences must be made about the incidence of disease (23).

Genetic risk information for common conditions is currently available to the general public only through consumer-oriented personal genomics companies, and the introduction of genetic risk information for common complex diseases into clinical care is likely to be slow. Understanding who wants genetic risk information and their reasons for wanting it may help clinicians tailor communication to maximize its relevance and satisfy patients' needs. Interest in genetic risk information is affected by individual beliefs, interpersonal relationships, and social and environmental factors. Nevertheless, trends suggest that the following groups may be more likely to seek genetic risk assessments for common disorders: women (33, 89), Caucasians (1, 89), individuals with a family history of disease (90), and adults with more education (30, 86). The last group is particularly notable given the complexity of genetic risk information. The public often scores slightly better than random chance on genetic knowledge scales (17, 92). Moreover, the way genetic information is commonly communicated compounds these challenges; some personal genomics company websites, for instance, are written at a grade-15 education level (63).

Understanding the reasons for pursuing a genetic risk assessment for common disorders may also help maximize the relevance of tailoring communication. In the REVEAL Study, most participants endorsed multiple reasons for seeking genetic risk assessment for AD (mean = 7.2), including the need to arrange personal affairs, curiosity, and the need to prepare one's family for the possibility of AD (89). Although obtaining information about prevention is the most popular perceived benefit of a genetic risk assessment for AD (19), these findings highlight that individuals who seek genetic susceptibility testing may not consider direct medical benefits their only objective. In fact, most research on genetic risk assessments has found that patients perceive benefits to testing that are unrelated to that testing, whether the context is targeted *BRCA1/2* testing to identify breast/ovarian cancer risk (5, 14) or general genome screening to identify risk for multiple common conditions (41).

Conducting Genetic Testing Safely in an Abbreviated Manner

Genetics providers already report feeling strained by current patient care demands and are streamlining their practices (104). Currently, there are approximately 1,500 certified clinical geneticists and 3,000 certified genetic counselors practicing in the United States (3, 4). To compensate, a number of recent studies have used nonspecialists (e.g., a health educator) or have tried alternative formats (e.g., the Internet) to communicate genetic risk information (10, 62, 75). Whether such methods compromise the ability of patients to understand or cope with the information is unclear. The second REVEAL Study trial was one of the few studies to explore modifications to pre-test education as well as risk disclosure. Participants randomized to a "condensed protocol" arm were mailed an educational brochure to replace an in-person educational session, and subject-led question-and-answer time replaced structured genetic-counselor-led discussion prior to genotyping. Analyses found that, in addition to including one fewer in-person encounter, the condensed protocol reduced clinician time from 77 minutes to 34 minutes. On measures of information recall

and understanding, participants receiving condensed education performed no worse than partici-
pants receiving extended education (87). Furthermore, preliminary analyses suggest that when test
results were disclosed by a genetic counselor, subjects receiving the condensed protocol reported
no greater post-test anxiety, depression, or test-related distress at one year after disclosure than did
subjects receiving the original extended protocol. However, when test results were communicated
by a nongeneticist physician, *APOE* ε4 carriers receiving the condensed protocol had greater
test-related distress scores at six weeks after disclosure. Further work will need to explore whether
differences between physician and genetic-counselor disclosures are due to differences in training,
differences in rapport (genetic counselors also acted as study coordinators and were younger and
female, whereas physicians were older and male), or other factors. Cautious approaches are also
warranted given that patients frequently forget key pieces of information shortly after education
or disclosure of test results (31, 81). Nevertheless, results suggest that educational burdens may
be reduced without affecting psychological outcomes or understanding (47).

The third REVEAL Study trial examined another way of streamlining genetic risk disclosure
by comparing telephone disclosure against in-person disclosure. Preliminary analyses suggest that,
although there were no differences between disclosure methods in terms of anxiety, those receiving
results via telephone had higher scores on scales of depression and test-related distress one to six
weeks after disclosure. Results suggest that telephone disclosure may not address patients' short-
term psychological needs as well as in-person disclosure does, and patients of concern (e.g., those
with elevated depression prior to testing) may benefit from face-to-face discussions when receiving
results. At the same time, all scores on psychological outcomes were well below clinical cutoffs
for concern, and measures of information recall and understanding may have been better among
those who received telephone disclosure. Similar, if not more favorable, results have been reported
from initial work related to the use of videoconferencing technologies during risk disclosure (43,
66, 108, 109).

Should Incidental Information Be Disclosed?

The advent of genome sequencing technologies has led to an emerging debate about whether
and (if so) how to disclose genetic risk information incidental to the original purpose of testing. A
primary aim of the third REVEAL Study trial was to examine this question empirically by disclosing
an unexpected element during risk assessment for AD: that the *APOE* ε4 allele is also associated
with increased risk for cardiovascular disease. Preliminary analyses suggest that this additional
information may actually help individuals cope with indications of increased risk for disease and
may motivate them to make additional improvements to health behaviors. Results suggest that
disclosure of incidental genetic information can have unexpected benefits with respect to coping
and disease prevention (20, 21).

How might communicating genetic risk information facilitate behavior change? Chao and
colleagues (16) used data from the first REVEAL Study trial to examine this issue empirically.
Subjects who learned they were *APOE* ε4 positive were more likely than those who learned they
were *APOE* ε4 negative or those who had received a nongenetic risk assessment to report an
AD-specific health behavior change. In fact, approximately half (52%) of those who learned they
had an increased genetic risk of AD reported a health behavior change based on their genetic test
results, such as changes made to medications, vitamins, diet, or exercise. Vernarelli and colleagues
(99) explored these findings further, focusing on dietary supplement use in the second REVEAL
Study trial. Subjects who were *APOE* ε4 positive were nearly five times more likely to report a
change in dietary supplement use compared with subjects who were ε4 negative.

Results from the REVEAL Study have also shown that genetic susceptibility testing may affect
insurance purchasing. In the first REVEAL Study trial, *APOE* ε4–positive subjects were almost

six times more likely to report altering their long-term care insurance coverage compared with those who received a nongenetic risk assessment (106). Similarly, in the second REVEAL Study trial, subjects with one *APOE ε*4 allele were 2.3 times more likely to increase their long-term care insurance coverage or report that they plan to do so compared with those with an *APOE ε*3/*ε*3 genotype (97). Use of self-reported outcomes, examination of self-selected populations, and examination of an emotionally charged condition like AD limit the generalizability of behavioral findings, but REVEAL Study data support the possibility that genetic risk information can motivate behavior change.

Such findings run counter to data from other reports on genetic susceptibility testing, however. Communicating an increased genetic risk for lung cancer can motivate short-term smoking cessation, but the effects disappear over time (27, 94). High-penetrance mutations associated with various forms of cancer often increase screening rates, but genetic tests examining markers that have moderate to weak associations with common complex conditions have shown little ability to motivate behaviors such as smoking cessation, dietary changes, or improved physical activity (76). Thus, general pessimism surrounds the idea that genetic risk information will evolve into an effective tool for health promotion.

Considered against REVEAL Study findings, however, the inconsistencies suggest that the field may be addressing the wrong question. It may be a question not of whether genetic risk information can motivate health behavior changes, but rather under what conditions it might do so. Some experts have suggested that more effective approaches to communicating genetic risk information would capitalize on the ways this information differs from other types of risk information. Group-level interventions are frequently more successful than individual-level behavioral interventions, suggesting that greater benefits might accrue from tailoring genetic risk communication to families rather than individuals (76). Individuals receiving genetic risk information already seem to understand the familial implications: Of the more than 80% of REVEAL Study subjects who reported telling others their genetic test results, 64% reported telling a family member (6). Such interventions have not been tested but represent fertile ground for future work as genetic information becomes more commonplace.

Accepting the Limited Ability of Genetic Testing to Change Perceptions

Genetic profiling can change perceptions and reduce uncertainty about disease risk (64), but it is important to keep in mind that it may not be the most important determinant of them. In 2010, Linnenbringer and colleagues (69) analyzed REVEAL Study participants who accurately recalled their communicated risk estimate and found that nearly half believed their actual risk was different from what they were told. Among those who disagreed with the given lifetime risk estimate, the majority (69%) reported that they thought their risk was higher than what was disclosed. Those who perceived a greater baseline AD risk were more likely to believe their actual risk was greater than the risk indicated by the genetic risk assessment. These findings build on prior work examining nongenetic risk assessments, family history analyses, and genetic tests for deterministic mutations associated with cancer that showed that risk perceptions are resistant to change (7, 52, 102). Genetic susceptibility information is not the sole determinant of risk perceptions, and individuals integrate genetic test results into existing beliefs about disease and well-being.

What Is the Impact of Using Genetic Risk Markers to Communicate About "Imminent Risk"?

The first three REVEAL Study trials examined disclosure of genetic risk information to asymptomatic adults, the vast majority of whom were unlikely to develop AD until well into the future.
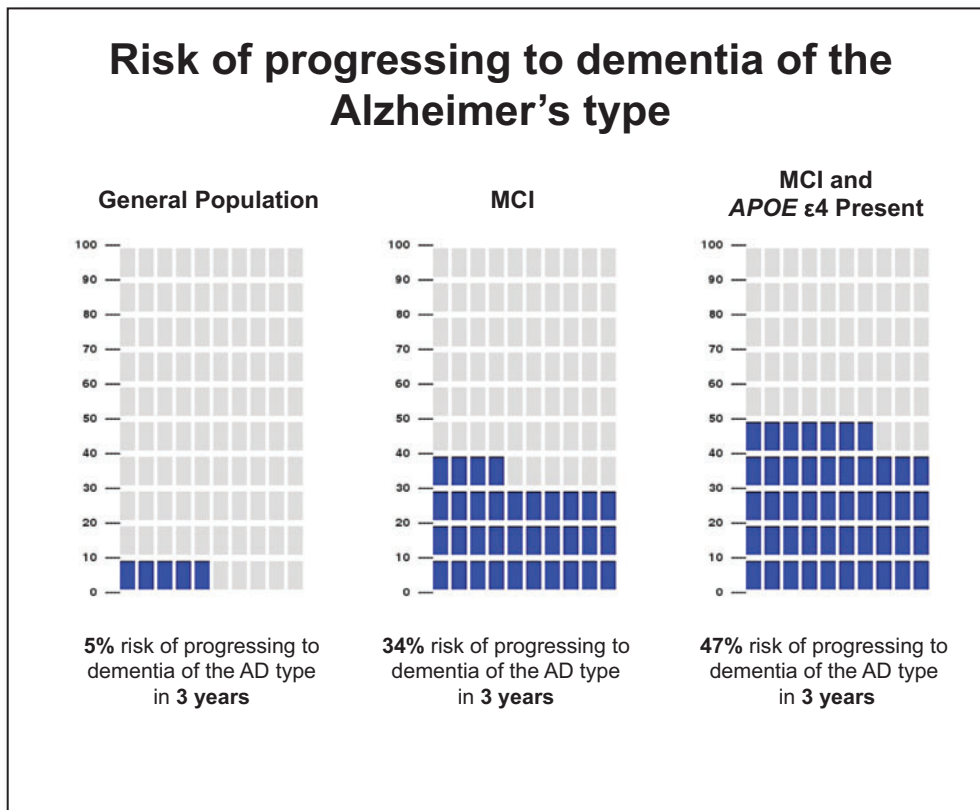
Figure 3

Sample risk result pictograph set from the fourth Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study trial. Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment.

The fourth REVEAL Study trial is currently under way, examining the safety and impact of genetic risk disclosure among individuals who already have mild cognitive impairment and are more imminently at risk of developing AD. **Figure 3** provides an example of a pictograph set used for risk presentation in this trial. The trial will also offer insight into how individuals respond to genetic risk information in the context of phenotypic information (65).

Impact of the REVEAL Study on Understanding of Genetic Risk Communication

The REVEAL Study was the first study of genetic susceptibility testing for common complex diseases to empirically evaluate issues in genetic risk communication using randomized clinical trials. Although this study examined these topics in the context of single-gene testing to determine risk for a specific disease, several key points may be generalizable when considering the impact of communicating genomic risk information from more sophisticated technologies (e.g., SNP arrays that examine markers for multiple conditions, whole-genome and whole-exome sequencing).

First, many people are interested in this information even if there is nothing they can do to reduce their risk. Although health care professionals may value medical utility and clinical actionability as important reasons for offering a genetic susceptibility test, we must recognize that the public may attach substantial personal utility to such information. Second, communicating an increased genetic risk for a terrifying, incurable, adult-onset disease can be done safely by modifying protocols developed for deterministic conditions like Huntington's disease, and protocols can even be streamlined without compromising the understanding or psychological well-being of test recipients who volunteer for such studies. Finally, the way individuals interpret genetic risk information is complex and often unexpected. The fact that many REVEAL Study participants did not take the provided information at face value and the way in which the disclosure of incidental cardiovascular disease associations motivated behavior change and improved coping are just two examples of the complex ways individuals internalize genetic risk information.

During the REVEAL Study, several direct-to-consumer companies arose offering the public the opportunity to obtain genetic risk information for hundreds of diseases or conditions at once, thus making the REVEAL Study particularly relevant to the controversial discussion that arose (55). Numerous commentators have raised questions about the ethics and regulation of direct-to-consumer personal genomics services (11), the potential for misunderstanding or psychological harm, and the potential for such information to increase unnecessary medical costs (78). However, these companies have also created novel ways for communicating vast amounts of genetic risk information, utilizing the Internet as a large-scale avenue for disclosure, and thus they provide a great opportunity to study the impact of communicating this type of information. Partnerships between these private companies and academic institutions have stimulated multiple research initiatives across the United States to study how individuals respond to, understand, and utilize hundreds of pieces of genetic risk information (15, 66a), including the Impact of Personal Genomics (PGen) Study to measure the pre- and post-test impact of personal genomics services. Studies to date suggest that learning this type of risk information does not result in short-term changes in psychological health, diet, or exercise behavior or the use of screening tests (10) but may modestly influence risk perception and worry (56). Other high-profile recent and ongoing research endeavors to further elucidate how the public understands and utilizes genetic risk information include the Coriell Personalized Medicine Collaborative (62) and the Multiplex Initiative led by scientists at the National Human Genome Research Institute (75). Results from the Coriell Personalized Medicine Collaborative indicate that early adopters of such a service are motivated by their own curiosity and to find out information that directly benefits their own health (41) and that participants have a reasonable understanding of the genomic risk information they received (62).

RISK COMMUNICATION TO PROMOTE POSITIVE HEALTH OUTCOMES

Investigators around the world are examining novel methods for communicating health risk information to promote positive health outcomes. Although genetic information may or may not be sufficient to promote positive behavior changes on its own (72), it is becoming increasingly relevant when considering an individual's risk of disease. Experts in risk communication have identified problems with accurate risk communication among both patients and physicians. For example, authors of a New Zealand study of cardiovascular disease risk communication identified that telling a person who smokes that he or she has a 10% risk of a cardiovascular event is unlikely to motivate the person to stop smoking unless the person is also told what the absolute risk of a cardiovascular event would be after quitting smoking (103). Similarly, telling a person who smokes that his or her risk of a cardiovascular event is twice that of nonsmokers is relatively unhelpful

unless the absolute risk of a cardiovascular event in nonsmokers is also communicated. In this study, the authors developed a program for communicating cardiovascular disease risk called Your Heart Forecast, which incorporates both absolute and relative risk information to advise patients of their risk of cardiovascular disease over time, how that risk compares with that of other individuals of the same age and of different ages, and how risk may be modified as risk factors change over time (103). Unlike Your Heart Forecast, empirical studies of genetic risk communication over the past decade have examined whether genetic risk information influences behavior change but have generally focused on communicating a single risk figure, rather than showing how risk may be lowered as behavior changes. This may be due to an early and now-dissipating perception that genetic risk information alone may be highly deterministic and thus powerful enough to influence behavior.

Another example of using genetics to instigate behavior change is the ongoing Personalized Risk Estimator for Rheumatoid Arthritis (PRE-RA) Family Study. This study is funded by the National Institutes of Health to examine the behavioral impact of communicating a risk prediction model for rheumatoid arthritis. The risk prediction model incorporates both nonmodifiable (age, sex, family history, and genetic risk score) and modifiable (smoking, periodontitis, and fish intake) risk factors. It also utilizes biomarkers by testing for autoantibodies associated with rheumatoid arthritis. Unlike risk calculators aimed at physicians for prevention or treatment, the PRE-RA risk tool is modeled after Your Disease Risk (**http://www.yourdiseaserisk.wustl.edu**), an easily navigable online interface, and is aimed directly at participants to identify behaviors that they can modify to change their own risk for rheumatoid arthritis (**Figure 4**).

PREPARING FOR THE FUTURE

The era of genomic medicine has arrived (44). Laboratories around the country are offering Clinical Laboratory Improvement Amendments (CLIA)–certified whole-genome and whole-exome sequencing as a clinical service (46). Furthermore, access to sequencing is expected to become increasingly available to the general public via personal genomics companies. As the cost of DNA sequencing decreases, the technology will become even more accessible.

As the genomic era makes available vast amounts of genetic data on each individual, a need emerges to effectively communicate information about hundreds of genetic risk factors to individuals or their health care providers, as well as to prioritize important results to disclose if returning all results is not feasible (45). For these purposes, current models of genetic counseling and genetic risk communication are simply not scalable.

We believe that whole-genome and whole-exome sequencing will be used in many ways, including in two distinct and complementary situations. In generally healthy patients, physicians will use the results to gain insight into future health risks and to inform prevention and surveillance efforts, a category we refer to as general genomic medicine. In patients presenting with a family history or symptoms of a disease, physicians will use the results to interrogate particular sets of genes known to be associated with the disease in question, a category we refer to as disease-specific genomic medicine. How these differing contexts affect the communication of risk information derived from sequencing is an open question and the focus of ongoing research. Three of the authors of this article (D.M.L., K.D.C., and R.C.G.) are part of a team of more than 40 investigators currently conducting a project to develop a process to integrate whole-genome sequencing into clinical medicine and explore the impact on health outcomes in both primary and specialty care settings. In the MedSeq Project, we are randomizing physicians and their patients to receive clinically meaningful information derived from whole-genome sequencing as opposed to information from current standards of care (National Institutes of Health grant U01HG006500, ClinicalTrials.gov ID NCT01736566). Data from the MedSeq Project will

Figure 4

Sample results from the Personalized Risk Estimator for Rheumatoid Arthritis (PRE-RA) Family Study risk calculator.

provide critical insight about ways to communicate the wealth of risk information derived from DNA sequencing to enhance clinical care and maximize patient understanding and well-being.

This review highlights the need to draw on the collective wisdom gained through multidisciplinary perspectives when considering the communication of genetic risk information, whether from a single genetic marker or from hundreds of risk figures derived from genome sequencing data. As we embark on a new era of estimating and communicating genetic risk information, we should not only build on our past experiences, but also collaborate with risk communication colleagues in various disciplines to develop methods that can help integrate vast amounts of genetic risk information with nongenetic risk information to improve health outcomes.

SUMMARY POINTS

1. Communication of genetic risk information, integration of such information into individualized health care, and the consequences of both will rapidly broaden in scope and practice, as current and emerging technologies allow more individuals and their health care providers to access information about genetic makeup.

2. Communication of genetic risk information may be best practiced with insight into how individuals understand, perceive, and make decisions based on risk information daily, including both health- and non-health-related risk information and both genetic and nongenetic health risk information.

3. Evidence-based strategies for presenting all types of risk information include (*a*) presenting risk information in multiple formats while avoiding qualitative modifiers, (*b*) being conscious of framing biases and framing risk in multiple ways, (*c*) using carefully chosen graphics, (*d*) using a small denominator (from 50 to 100) when possible, (*e*) remembering that less is more, (*f*) paying attention to emotions that may influence perception and adoption of risk figures, and (*g*) engaging recipients in communication.

4. The REVEAL Study was the first study of genetic susceptibility testing for a common complex disease to utilize randomized trials in communicating genetic risk information, and some of these findings may be generalizable when considering the impact of communicating genomic risk information for other conditions.

5. Investigators in the field of genetic risk communication should not only build on past experiences but also collaborate with risk communication colleagues in various disciplines to develop methods that can best achieve positive health outcomes.

DISCLOSURE STATEMENT

ACKNOWLEDGMENTS

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