Public Perceptions of Disease Severity but Not Actionability Correlate with Interest in Receiving Genomic Results: Nonalignment with Current Trends in Practice

Kristi D. Graves\textsuperscript{a} Pamela S. Sinicrope\textsuperscript{b} Jennifer B. McCormick\textsuperscript{c} Yingjun Zhou\textsuperscript{a} Susan T. Vadaparampil\textsuperscript{d} Noralane M. Lindor\textsuperscript{b}

\textsuperscript{a}Lombardi Comprehensive Cancer Center, Georgetown University, Washington, D.C., \textsuperscript{b}Department of Health Sciences Research, Mayo Clinic, Scottsdale, Ariz., \textsuperscript{c}Biomedical Ethics Program, Divisions of General Internal Medicine and Health Care Policy and Research, Mayo Clinic, Rochester, Minn., and \textsuperscript{d}Moffitt Cancer Center, Tampa, Fla., USA

**Abstract**

**Purpose:** Frameworks highlighting disease actionability and severity are evolving to address the need to organize results from genome-wide analyses. This approach represents a paradigm shift from consultations focused on one or more genes to multiple genes for multiple disorders. Empirical input from the general population is lacking, yet seems essential for understanding how to maximize patient autonomy and satisfaction in the decision-making process. **Methods:** We conducted a cross-sectional online survey with a representative sample of 900 US adults and assessed the participants’ perceptions and attitudes toward disease actionability and severity, ranking hypothetical scenarios for these properties, and explored correlations with interest in learning test results. **Results:** Most respondents (>85%) rated actionability and severity as useful concepts; 46.6% indicated actionability alone would be adequate for decision making. Over half of them (53.8%) reported being very/extremely confident in their ability to score for actionability and severity. The participants’ scoring of medical scenarios varied significantly between individuals. Scores for severity but not actionability were correlated with interest in learning genetic results. Subsets of the respondents projected wanting all results (30%) or no results (16%). The use of expert-created lists was acceptable to 43%. **Conclusions:** The respondents from the general population were confident in making their own decisions. The responses suggested different priorities than current expert-driven approaches. The emphasis on binning genes may be missing a complementary, simplifying approach of grouping patients based upon their all/no interest in genomic results. This study illuminates important differences between the general public and genetic experts.

© 2015 S. Karger AG, Basel

**Introduction**

The practice of genetic medicine continues to shift from consultations focused on one or a few genes for a single disorder to a simultaneous consideration of mul-
tiple genes for multiple disorders. New sequencing technologies that permit a rapid, inexpensive, genome-wide analysis (generically called next generation or ‘nextgen’ sequencing) are being integrated into the clinical practice to solve diagnostic dilemmas, to compare tumor and germline DNA to identify potential therapeutic targets, and to assess disease risk among healthy individuals.

In recent years, several frameworks have evolved to start to guide genetics professionals returning genetic test results to patients, largely based on the concepts of actionability and disease severity. For example, the initial American College of Medical Genetics (ACMG) recommendations for the return of incidental findings included a universal disclosure of pathogenic mutations for 56 genes selected by experts as being clinically actionable and of high penetrance [1, 2]. Another approach by Berg et al. [3] is to bin similar disorders according to the level of clinical actionability/utility: Bin 1 includes genes with a reasonable suggestion of beneficial interventions (n = 161 genes); Bins 2a and b are genes which are clinically valid but not actionable in terms of definable preventive measures or treatment (n = 1,855 genes), and Bin 3 includes genes with an unknown role in human disease. Rather than prebinning genes, Jarvik et al. [4] developed guiding principles for the return of individual genomic research results that include actionability with a participant’s right to refuse results that are offered. In an ethical deliberation of the role of disease characteristics in the disclosure of personal genome testing results, Bunnik et al. [5] identified 4 relevant disease characteristics in susceptibility testing as follows: severity, actionability, age of onset, and psychiatric versus somatic diseases. Our team at the Mayo Center for Individualized Medicine also undertook a multidisciplinary binning process which was briefly compared/contrasted to Berg’s bins, demonstrating overlap but also differences [6].

The current research on returning genomic results yields the recurrent themes of actionability and disease severity [5, 7, 8]. To date, definitions of clinical actionability or severity have been provided by expert review or consensus procedures [2, 3, 9–11]. One study showed good concordance between genetic experts over whether classical conditions, such as *BRCA1* mutations, were clinically actionable [2, 10] but challenges in reaching consensus, even among experts, for most other clinical situations [3, 12–14]. Significant research investment addressing this topic includes the Clinical Sequencing Exploratory Research Consortium [15].

Notably, none of the existing binning processes include broad-based input from the general population – the individuals who are most likely to be confronted with decisions about the return of genomic results. Robust empirical input from these key stakeholders on their perceptions of actionability and severity seems essential for understanding how to maximize patient autonomy in the decision-making process for the return of genomic results. While some research explores patient decision making for disclosure in clinical settings related to diagnostic exome sequencing [11, 16], a broader sample of people unselected for clinical phenotype has not been tapped.

Guided by conceptual frameworks from the Health Belief Model [17] and Social Cognitive Theory [18, 19], we aimed to (1) describe the factors that people in the general public consider important to the concepts of actionability and severity of disease in the context of genetic testing; (2) explore the relationships between clinical, attitudinal, health belief, and sociodemographic characteristics and the public’s perceptions of actionability and severity, and (3) describe how people score prototypical medical scenarios for actionability and severity and examine whether scoring relates to the intention to learn results.

### Materials and Methods

**Study Population**

In December 2013, we conducted an online survey with a sample of US adults using the YouGov opt-in panel [20]. YouGov, an online survey company (Palo Alto, Calif., USA), maintains a consumer panel of 1.2 million adults recruited through web-based advertising campaigns, online advertisements, and mail and telephone to web recruitment campaigns. The YouGov panel is large and demographically diverse, which allows for sample matching – a model-based approach to non-probability-based sampling. The sample matching method is best known for its application in nonrandomized medical studies [21]. YouGov constructs representative samples with a 2-stage sampling design. First, a sample frame is constructed from the American Community Study [22] with additional data from the current population voter supplement, the Pew Research Religion & Public Life Project [23]. From this framework, YouGov draws a stratified random sample of people that is similar in size to the desired study sample. At a second stage, the sampling algorithm behind the proprietary sampling system searches the opt-in panel for participants who most closely match the individuals in the randomly drawn target sample. The algorithm invites 2–3 matches by age, race, gender, and education for every respondent in the target frame.

**Procedures**

**Overview and Survey Design.** The Mayo Clinic Institutional Review Board determined that this study did not constitute research involving human subjects as defined under 45 CFR 46.102, as data were de-identified. The multidisciplinary study team developed a...
Perceptions about Disease Actionability and Severity

After the respondents viewed several brief PowerPoint videos embedded in the survey (online suppl. material A), similar to what a genetic counselor might use to briefly introduce genetic concepts in a clinic setting, we inquired whether they understood the description of actionability. In the videos and narrative, the term ‘actionable’ was defined as ‘actions that can be taken to prevent or treat a medical condition’ or, alternatively, ‘medical treatments that can protect a person’s health or return a person to ideal health’. Slides 10–14 in online supplement material A show the definitions of the actionability categories and provide examples of disorders within each category.

We also asked whether grouping medical conditions by severity would help people decide what conditions they may or may not want to learn about; whether they thought people would agree on how severe disorders are, and how important considering severity would be in deciding to learn about genetic tests. They were asked to score specific reasons for their relevance in deciding how to rank genetic conditions by severity. The role of disease penetrance was approached by asking the participants to score perceived severity for a condition if the risk for sudden death was 1, 5, or 10% (online suppl. material A).

Outcome Variables for Multivariate Analysis

Actionability. We assessed perceptions of disease actionability with the item ‘When deciding which genetic testing results you would want to know about, how useful would it be for those medical conditions to be classified by how “actionable” that condition is?’ with responses made on a 4-point Likert scale (1 = extremely to 4 = not at all).

Disease Severity. Disease severity was assessed with the question ‘When deciding which genetic testing results you would want to know about, how useful would it be for those medical conditions to be classified by how “severe” that condition is?’ with responses made on a 4-point Likert scale (1 = extremely to 4 = not at all).

Interest in Learning Genomic Test Results. We asked the participants to provide feedback on the types of genetic conditions they would hypothetically want to learn about based upon a combined assessment of actionability and severity across a matrix of 3 ranges of severity and 4 groups of actionability. In addition, for conditions of moderate severity, we explored how involvement of particular body parts or functions (e.g., eyes, seizures, bones, heart diseases, and kidney diseases) might hypothetically influence people’s interest in receiving genomic test results.

Hypothetical Scenarios. Finally, to assess the respondents’ perceptions of actionability and severity and to correlate that with their interest in learning genomic test results, we asked them to respond to a series of scenarios. Eighteen medical scenarios were developed that included prototypical medical/genetic conditions for the participants to review and then score (‘bin’). The scenarios represented a broad range of potential conditions and were designed to capture the uncertainty associated with the available interventions (online suppl. material B). To reduce the participants’ burden, each participant was randomly assigned 9 of the possible 18 scenarios.

Analyses

We calculated descriptive statistics of the continuous variables as means and standard deviations and reported categorical variables as number of observations and percentages. For our primary
outcomes of the importance of actionability and severity in the interest in learning genomic test results, we created dichotomous outcomes with the participants’ ratings of ‘slightly’ or ‘not at all’ compared to combined ratings of ’very’ or ’extremely’. We opted for these dichotomous outcomes because in both outcomes the majority (~85%) of the participants chose ‘very’ or ’extremely’ with 40–45% in each group, whereas only 15% in total chose ‘slightly’ or ‘not at all’. The distribution provided a clear distinction between ‘very’/’extremely’ and ‘slightly’/’not at all’ and indicates high homogeneity in population characteristics within the 2 groups.

We conducted bivariate analyses using χ² tests for categorical variables and t tests for continuous variables. We used Fisher’s exact tests for contingency tables with low cell counts (<5) for categorical variables and Wilcoxon signed-rank tests for continuous variables with skewed distributions. We selected variables for the multivariate analyses based on our theoretical models, existing literature regarding demographic and psychosocial correlates of genetic testing, and findings from our bivariate analyses that were significant at the 0.05 level. Logistic regression models were used for multivariate analyses to further evaluate the association between adjusted predictors and outcomes. In all analyses, samples were weighted to match the distribution of the general US population in age, gender, race/ethnicity, marital status, and years of education completed. Responses with missing items were not included in the analyses. Analyses were conducted in SAS 9.3 (Cary, N.C., USA). All p values were 2-sided, and p values <0.05 were considered statistically significant.

Results

Respondents’ Characteristics

Nine hundred respondents completed the questionnaire (mean age 45 years, SD = 17, range 18–70). The majority (82.9%) reported they had no experience with genetic testing. Other characteristics are shown in table 1.

Aim 1: Describe the Factors That People in the General Public Consider Important to the Concepts of Actionability and Severity of Disease in the Context of Genetic Testing

The majority of the participants viewed both actionability (87%) as well as severity (85%) as useful when deciding what genomic results they might want to learn. Specific factors most participants (>70%) considered important to the perceptions of severity included loss of sensory, physical, and cognitive abilities and the possibility of death. Almost two thirds (~65%) of the participants rated the financial impact and the effect on those closest to them as important to the perceptions of disease severity. Less consistent were the respondents’ views of whether the risks to children or fertility were important when considering disease severity (table 2).

Most participants were moderately to extremely confident in their own ability to categorize disorders (89%), think about actionability when making decisions (88%), think about actionability and severity together (89%), and make a decision that is right for them as regards learning or not learning test results (91%). The respondents had mixed responses when asked whether they like the idea of a list prepared by experts for deciding what genetic test results they should be told (34% no, 40% yes, 26% unsure).

Aim 2: Explore the Relationships between Clinical, Attitudinal (Perceived Benefits, Self-Efficacy, Motivators), Health Belief (Perceived Salience, Perceived Risk), and Sociodemographic Characteristics and the Public’s Perceptions of Actionability and Severity

Actionability. In bivariate analyses, the following variables were statistically significantly associated with viewing actionability as important when making decisions about learning genetic test results: familiarity with genetic testing, perceived higher risk of heart disease, perceived salience of both genomic testing and having a healthy lifestyle, perceived benefits of testing and self-efficacy for managing results from genomic testing (p < 0.001; table 1). In multivariate analyses, viewing actionability as important to decisions about genetic testing was not associated with age, gender, race, marital status, education, childbearing status (yes/no), self-efficacy, or perceived risk of heart disease. In contrast, people who rated themselves as familiar with genetic testing were 2.33 times more likely to rate actionability as extremely or very important in deciding what results to learn compared to those with little or no genetic knowledge (p = 0.004). Perceived benefits of genomic testing – measured as importance of genomic results for family health – were significantly associated (p < 0.001) with ratings of actionability as very useful. Similarly, perceived salience of a healthy lifestyle (p < 0.003) and perceived salience of genetic testing (p < 0.007) were positively associated with greater endorsement of actionability as extremely/very useful in decision making (table 3).

Severity. In bivariate analyses, the participants’ responses of viewing disease severity as important for learning genetic test results were statistically significantly associated with familiarity with genetic testing, perceived higher risk for heart disease and cancer, perceived salience of genetic testing, perceived salience of a healthy lifestyle, self-efficacy, and perceived benefits of genetic testing (table 1). In multivariate analyses, views of sever-
Table 1. Demographics and bivariate associations of actionability and severity as important for return of genomic test results

| Variable                        | Actionability | Severity | Total sample (n = 900) |
|--------------------------------|---------------|----------|------------------------|
|                                | not at all/slightly important | very/extremely important | not at all/slightly important | very/extremely important |
| Age, years                     | 46.2±17.2     | 45.4±17.0| 46.3±15.7              | 45.3±17.2              | 45.4±16.9              |
| Education                      |               |          |                        |                        |                       |
| ≤High school                   | 50 (42)       | 317 (41) | 57 (41)                | 312 (41)               | 367 (41)               |
| >High school                   | 68 (58)       | 463 (59) | 80 (59)                | 451 (59)               | 531 (59)               |
| Gender                         |               |          |                        |                        |                       |
| Male                           | 64 (54)       | 376 (48) | 68 (50)                | 375 (49)               | 443 (49)               |
| Female                         | 53 (46)       | 404 (52) | 59 (50)                | 388 (51)               | 457 (50)               |
| Race/ethnicity                 |               |          |                        |                        |                       |
| Non-Hispanic White             | 73 (62)       | 515 (66) | 102 (74)              | 486 (64)               | 588 (65.3)             |
| Non-Hispanic Black             | 17 (14)       | 87 (11)  | 8 (6)                 | 96 (13)                | 104 (11.5)             |
| Hispanic                       | 13 (11)       | 120 (15) | 15 (11)               | 121 (16)               | 136 (15.1)             |
| Other race                     | 15 (13)       | 58 (7)   | 12 (9)                | 60 (8)                 | 72 (8.1)               |
| Marital status                 |               |          |                        |                        |                       |
| Married                        | 64 (54)       | 399 (51) | 79 (57)                | 387 (51)               | 466 (51.7)             |
| Not married                    | 54 (46)       | 381 (49) | 58 (43)                | 376 (49)               | 434 (48.3)             |
| Parental status                |               |          |                        |                        |                       |
| Yes/planning children          | 65 (56)       | 444 (57) | 78 (57)                | 432 (57)               | 509 (56.6)             |
| No/not planning children       | 52 (44)       | 331 (42) | 59 (43)                | 324 (42)               | 383 (42.5)             |
| Knowledge of genetic testing   |               |          |                        |                        |                       |
| Yes                             | 81 (69)       | 646 (83) | 98 (71)                | 630 (83)               | 727 (80.8)             |
| No                              | 36 (31)c      | 134 (17)c| 39 (29)b              | 133 (17)b              | 173 (19.2)             |
| Experience with genetic testing |               |          |                        |                        |                       |
| Yes                             | 92 (78)       | 654 (84) | 115 (83)               | 631 (83)               | 746 (82.9)             |
| No                              | 26 (22)       | 126 (16) | 23 (17)               | 132 (17)               | 154 (17.1)             |
| Perceived risk of cancer       |               |          |                        |                        |                       |
| High                            | 23 (20)       | 202 (26) | 30 (22)                | 195 (26)               | 226 (25.1)             |
| Low                             | 31 (27)       | 189 (24) | 25 (18)               | 195 (26)               | 220 (24.5)             |
| Same                            | 58 (49)       | 335 (43) | 74 (54)               | 319 (42)               | 393 (43.7)             |
| Had cancer                      | 5 (4)         | 50 (6)   | 8 (6)                 | 47 (6)                 | 55 (6.1)               |
| Perceived risk of heart disease |               |          |                        |                        |                       |
| High                            | 26 (22)       | 225 (33) | 25 (18)               | 255 (33)               | 281 (31.2)             |
| Low                             | 37 (32)       | 180 (23) | 35 (26)b              | 183 (24)b              | 218 (24.2)             |
| Same                            | 48 (41)       | 320 (41) | 66 (48)               | 302 (40)               | 368 (40.9)             |
| Had heart disease               | 4 (3)         | 24 (3)   | 8 (6)                 | 20 (3)                 | 28 (3.1)               |
| Current health state            |               |          |                        |                        |                       |
| Poor to fair                    | 39 (33)       | 256 (33) | 37 (27)               | 258 (34)               | 295 (32.8)             |
| Good to great                   | 76 (65)       | 524 (67) | 97 (71)               | 503 (66)               | 600 (66.7)             |
| Salience of healthy lifestyle   |               |          |                        |                        |                       |
| Not at all/little               | 42 (36)c      | 91 (12)c | 39 (29)c              | 94 (12)c               | 133 (14.8)             |
| Somewhat/very                   | 73 (62)       | 689 (88) | 95 (70)               | 667 (87)               | 762 (84.7)             |
| Perceived benefits of genomic testing |            |          |                        |                        |                       |
| 0 benefits                      | 70 (59)c      | 100 (13)c| 69 (51)b              | 103 (13)b              | 172 (19.1)             |
| 1–2 benefits                    | 29 (25)       | 289 (38) | 47 (34)               | 281 (37)               | 327 (36.4)             |
| 3 benefits                      | 18 (16)       | 382 (49) | 21 (15)               | 380 (50)               | 401 (44.5)             |
| Confidence in making decisions about genomics |       |          |                        |                        |                       |
| 3.2±1.1 b                      | 3.7±0.9b      | 3.4±1.1  | 3.7±0.9               | 3.6±0.9                |                       |
| Perceived salience of genomic testing |           |          |                        |                        |                       |
| 4.0±1.2 c                      | 5.2±1.2c      | 4.1±1.4c | 5.2±1.8c              | 5.0±1.3                |                       |

Values represent mean ± SD or n (%). Some percentages do not add up to 100% due to a small amount of missing data (≤6 people; 0.6%). a p < 0.05; b p < 0.01; c p < 0.0001.
ity as important were not related to age, gender, race/ethnicity, marital status, education, childbearing status, or self-efficacy. However, the respondents with a higher perceived risk of heart disease were more likely to rate severity as extremely or very useful than the respondents with a lower perceived risk of heart disease (p = 0.020). Other factors that were statistically significantly related to perceptions of severity as useful in the context of genetic testing decisions including evaluating genetic information for family members (p < 0.001), reporting own health as ‘good’ to ‘great’ (p = 0.039), perceived salience of a healthy lifestyle (p = 0.002), and perceived salience of genetic testing (p < 0.001; table 3).

Aim 3: To Describe and Evaluate People’s Perceptions of Disease Severity and Actionability and Their Hypothetical Decisions about whether or Not to Learn Genomic Testing Results

Interest in Genomic Test Results. When considering severity and actionability unlinked to clinical descriptions of actual disorders, the interest in learning genomic results was lowest for a disorder of low severity that was not curable or preventable (35%) and highest for a disorder of moderate severity that was curable/preventable (71%; disorder of the eye; table 4). Overall, when unlinked to clinical descriptions of disorders, the interest in learning genomic results increased as the level of actionability increased, with close to two thirds of the respondents interested in learning results across the range of disease severity levels. For high severity disorders, we found only a 10% difference in interest in learning about genomic test results when actionability ranged from curable (63.8% interested in results) to incurable (53.6% interested in results; table 4). In a separate question in which disease severity was defined as moderate and different body parts/functions were listed, the interest in results varied (online suppl. table C).

Respondent Scoring of Clinical Scenarios. Twelve of the 18 disorders were scored as high severity by more than 40% of the responders (online suppl. material B; fig. 1). Of the 13 disorders that could be scored for actionability, 5 were classified as mostly actionable by the majority of the participants (>50%), while 8 scenarios showed a fairly even split between being assigned as mostly actionable or mostly not actionable. The percentage of the respondents whose desire to learn the results was ‘extremely likely’ ranged from 29% for craniofacial anomaly to 52% for childhood neurodegenerative disorder, which is also the disorder with the highest proportion of the participants rating it as severe (87%); this disorder was defined for participants as not being actionable at all. The Cochran-Armitage trend test showed that high severity is significantly associated with the interest in knowing test results (p < 0.001), while actionability is not (p = 0.421). Subsets of the respondents reported not wanting any genetic test results (15.9%) or wanting all results (30%; online suppl. table D).

Discussion

We present some of the first empirical data from a broadly representative sample of the general US adult population regarding perceptions of actionability and severity of health conditions identified by genomic testing. Most respondents in our sample reported not having had any type of experience with genetic testing (83%), similar to rates in the general public. Studies representing non-expert views have most often focused on individuals with increased risk for specific genetic conditions; thus, our
findings provide a unique perspective. Further, our respondents, who reported limited experience with genetic testing, had the opportunity to view educational materials embedded within the survey to enhance their understanding of the key concepts within genomic medicine decision making, actionability, and severity.

The majority of the respondents viewed both actionability (87%) and severity (85%) as useful concepts when deciding what genomic results they might want to learn, suggesting that laypeople and clinicians agree that these constructs are important for thinking about genetic testing. Since actionability has played a more prominent role
in the binning literature to date and because scoring for severity is so subjective, we queried if people thought they could make decisions based on actionability alone; a slim majority were comfortable with this proposal. Clearly, the idea of severity is held as meaningful by many people even if difficult to neatly categorize. People were confident in their own ability to identify what was severe and actionable, to think about these concepts together, and to make their own decisions about learning results. Future research can examine how self-efficacy relates to decision satisfaction following testing and receipt of results. Less than half of the respondents indicated support for an expert-derived list of genes to be returned to patients. While not a universal embrace, these results support offering such a premade list as it may be appreciated by some patients. Future work can examine whether individuals who did not agree with the use of a pre-

Table 4. Interest in learning genomic test results: combining actionability and severity

| Level of actionability                      | Level of severity, % | Level of severity, % |
|---------------------------------------------|----------------------|----------------------|
| Curable/preventable                         | low severity moderate severity high severity |
| Mostly curable/preventable                  | 64.1 57.0–69.1 63.8 |
| Mostly not curable/preventable              | 58.3 56.1–71.4 60.7 |
| Not curable/preventable                    | 37.8 44.7–53.2 54.0 |
|                                            | 35.3 40.0–46.0 53.6 |

The range in the moderate severity column reflects responses to the listing of multiple different body parts/systems (see online suppl. table C).
made list would make different choices when faced with an actual decision.

Perceptions of the importance of actionability and severity were influenced by attitudes and health beliefs. Those familiar with genetic testing and having positive perceptions of genetic testing were more likely to rate actionability as a useful construct. Health care experts generally view actionability as important in informing decisions about the utility of genomic test results [5]; however, our results underscore the importance of providing enough education for patients to facilitate the comprehension of available choices [27, 28]. In the present survey, we used narrated PowerPoint videos as a proxy for genetic counseling on genomic testing, which the participants reported to be understandable, though no tests were conducted to verify this.

The respondents largely agreed that functional impairments of all types, the possibility of death, and financial impact of disease were important to perceptions of severity. They reported greater variability in perceived importance of risks to children or fertility. Future analyses will describe the demographics underlying these differences. The respondents with a higher perceived risk of heart disease, but not cancer, were more likely to rate severity as useful compared to the respondents with a lower perceived risk of heart disease. These findings differ from prior work in which perceptions of severity were uniform across conditions [29]. Perceptions of severity as important in genomic testing decisions appear to be more important for people with better perceived health.

For both actionability and severity, those who perceived genomic testing as beneficial were more likely to rate actionability and severity as very useful. This finding is consistent with studies done in the context of testing for hereditary diseases, as a primary motivation for genetic testing is the potential for personal and family benefit [30–33]. Those who rated living a healthy lifestyle as very important were also more likely to rate actionability as useful, suggesting that individuals who perceive greater control of their health through preventive behaviors (e.g., diet and exercise) are more likely to endorse the uptake of conditions with an intervention.

Across the 18 specific medical scenarios (online suppl. material B; fig. 1), the participants tended to score most items high on severity. This may reflect the nature of the conditions described, but it may also reflect that any deviation from ideal health can be viewed as a serious threat to wellness, particularly in a sample of adults unselected for having a personal or family history of disease. The reduced variability on perceptions of disease severity may limit the ability to meaningfully bin different diseases using this construct. Even after the respondents engaged in scoring the conditions, most still endorsed the concept of severity as useful. Further research is required to see if an actionability-only approach to binning provides sufficient granularity for those who are making decisions about learning genetic test results.

The participant ranking of actionability for specific medical scenarios showed a broad spread: many conditions (e.g., renal failure with dialysis with or without kidney transplantation) were almost evenly split as to whether people scored as mostly actionable or mostly not actionable. It could be argued that nonmedically trained people did not fully understand the available medical interventions; however, an alternative interpretation is that perceptions of interventions (e.g., organ transplant and prophylactic surgery) were viewed by some as quite actionable and by others as not restoring health sufficiently to qualify as actionable enough. Our results suggest that views of actionability in the general population are not concordant across individuals within the population so caution is needed in presenting choices to patients based on expert binning: the contents of those bins may align poorly with individual patient expectations of what is meant by actionability. Just as the respondents in the present study varied in their views of actionability, individual patients likely vary in how they understand and respond to explanations of actionability by genetics professionals or within genetic research contexts.

A limitation to the present study is the self-selection of the respondents through the YouGov online survey, thus presenting a possible sampling bias. Further research is needed to understand differences across different samples in public versus clinical perspectives on actionability. The literature on personal versus clinical utility/actionability may provide some direction on this potential misalignment. For example, some experts use the terms utility and actionability interchangeably [3], but the distinctions between the two constructs may be important at the individual level (e.g., “Is the information useful to me?” vs. “Is there some type of clinical action I can take based upon this information and is that action sufficient to address this condition?”).

Although it was not a primary aim of this paper to evaluate patient preferences in returning results per se, we were surprised by the low correlation between the interest in results and perceptions of actionability; more than half of the respondents would be interested in learning genetic test results for diseases considered severe regardless of the level of actionability. These findings contrast with
evidence from nongeneticist health care providers who viewed decisions about the return of incidental findings as largely dependent on clinical actionability [34]. Although subsets of the respondents wanted either none (16%) or all (30%) of the results, 54% wanted only some of the genomic test results. Perhaps the emphasis on binning genes is missing a complementary approach; the most efficient binning of nearly half the public could be based on people: the determination of which individuals are inclined to know everything they can and which individuals really do not want to look behind that curtain at all, reducing the counseling time and content for at least those groups. Additional work is needed to define best practices for conducting discussions with patients who promote meaningful autonomous decision making and customized result disclosure in this new era of genomic testing.

Acknowledgements

The authors would like to thank the study participants for their time and input and YouGov for the collaboration and survey administration. Funding for this study was provided by the Mayo Clinic Center for Individualized Medicine.

References

1 American College of Medical Genetics and Genomics: ACMG updates recommendation on ‘opt out’ for genomic sequence return of results. ACMG News. April 1, 2014. https://www.acmg.net/docs/Release_ACMGUpdatesRecommendations_final.pdf (accessed November 5, 2014).

2 Green RC, Berg JS, Grody WW, Kalia SS, Korf BR, Martin CL, McGuire AL, Nussbaum RL, O’Daniel JM, Ormond KE, Rehm HL, Watson MS, Williams MS, Biesecker LG; American College of Medical Genetics and Genomics: ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genet Med 2013;15:565–574.

3 Berg JS, Amendola LM, Eng C, Van Allen E, Gray SW, Wagle N, Rehm HL, DeChene ET, Dulik MC, Hisama FM, Burke W, Spinner NB, Garraway L, Green RC, Prows CA, Rehm HL, Sharp RR, Salama SW, Holm IA, Kullo IJ, Lehmann LS, McCarroll MA, Garraway L, Green RC, Plon S, Evans JP, Jarvik GP, Members of the CSER Actionability and Return of Results Working Group: Processes and preliminary outputs for identification of actionable genes as incidental findings in genomic sequence data in the Clinical Sequencing Exploratory Research Consortium. Genet Med 2013;15:854–859.

4 Jarvik GP, Amendola LM, Berg JS, Brothers K, Clayton EW, Chung W, Evans BJ, Evans JP, Fullerton SM, Gallego CJ, Garrison NA, Gray SW, Holm IA, Kullo IJ, Lehmann LS, McCarty C, Prows CA, Rehm HL, Sharp RR, Salama SW, Sanderson S, Van Driest SL, Williams MS, Wolf SM, Wolf WA; eMERGE Act-ROR Committee and CERC Committee, CSER Act-ROR Working Group, Burke W: Return of genomic results to research participants: the floor, the ceiling, and the choices in between. Am J Hum Genet 2014;94:818–826.

5 Bunnik EM, Schermer MH, Janssens AC: The role of disease characteristics in the ethical debate on personal genome testing. BMC Med Genomics 2012;5:4.

6 Lindor NM, Johnson KJ, McCormick JB, Klee EW, Ferber MJ, Farrugia G: Preserving personal autonomy in a genomic testing era. Genet Med 2013;15:408–409.

7 Burke W, Trinidad SB, Clayton EW: Seeking genomic knowledge: the case for clinical restraint. Hastings Law J 2013;64:1650–1664.

8 Burke W, Antommaria AH, Bennett R, Botkin J, Clayton EW, Henderson GE, Holm IA, Jarvik GP, Khoury MJ, Knoppers BM, Press NA, Ross LF, Rothstein MA, Saal H, Uhlmann WR, Wilford B, Wolf SM, Zimmern R: Recommendations for returning genomic incidental findings: We need to talk! Genet Med 2013;15:854–859.

9 Goddard KA, Whitlock EP, Berg JS, Williams MS, Webber EM, Webster JA, Lin JS, Schrader KA, Campos-Outcalt D, Offit K, Feigelson HS, Holombe C: Description and pilot results from a novel method for evaluating return of incidental findings from next-generation sequencing technologies. Genet Med 2013;15:721–728.

10 Green RC, Lupski JR, Biesecker LG: Reporting genomic sequencing results to ordering clinicians: incidental, but not exceptional. JAMA 2013;310:365–366.

11 Shahmirzadi L, Chao EC, Palmaer E, Parra MC, Tang S, Gonzalez KD: Patient decisions for disclosure of secondary findings among the first 200 individuals undergoing clinical diagnostic exome sequencing. Genet Med 2014;16:395–399.

12 Grove ME, Wolpert MN, Cho MK, Lee SS, Ormond KE: Views of genetics health professionals on the return of genomic results. J Genet Couns 2014;23:531–538.

13 Sheehan M: Reining in patient and individual choice. J Med Ethics 2014;40:291–292.

14 Yu JH, Harrell TM, Jamal SM, Tabor HK, Bamshad MJ: Attitudes of genetics professionals toward the return of incidental results from exome and whole-genome sequencing. Am J Hum Genet 2014;95:77–84.

15 Gray SW, Martins Y, Feurman LZ, Bernhardt BA, Biesecker BB, Christensen KD, Joffe S, Rini C, Veenstra D, McGuire AL; CSER Consortium Outcomes and Measures Working Group: Social and behavioral research in genomic sequencing: approaches from the Clinical Sequencing Exploratory Research Consortium Outcomes and Measures Working Group. Genet Med 2014;16:727–735.

16 Bennett CS, Trinidad SB, Fullerton SM, Patrick D, Amendola L, Burke W, Hisama FM, Jarvik GP, Regier DA, Veenstra DL: Return of incidental findings in genomic medicine: measuring what patients value – development of an instrument to measure preferences for information from next-generation testing (IMPRINT). Genet Med 2013;15:873–881.

17 Glanz K, Rimer BK, Lewis FM: Health Behavior and Health Education: Theory, Research, and Practice, ed 3. San Francisco, Jossey-Bass, 2002.

18 Bandura A: Human agency in social cognitive theory. Am Psychol 1989;44:1175–1184.

19 Bandura A: Social cognitive theory: an agentive perspective. Annu Rev Psychol 2001;52:1–26.

20 YouGov.com. https://today.yougov.com/ opi/ (accessed November 5, 2014).

21 Rubin DB: Matched Sampling for Causal Effects. Cambridge, Cambridge University Press, 2006.

22 United States Census Bureau: American Community Survey. http://www.census.gov/acs/www/ (accessed November 5, 2014).

23 Pew Research Center: Pew Research Religion & Public Life Project. http://www.pewforum.org/ (accessed November 5, 2014).

24 Rubin HJ, Rubin I: Qualitative Interviewing: The Art of Hearing Data. Thousand Oaks, Sage Publications, 1995.

25 Mateau TM, Weinman J: Self-regulation and the behavioural response to DNA risk information: a theoretical analysis and framework for future research. Soc Sci Med 2006;62:1360–1368.
26 Lipkus IM, Kuchibhatla M, McBride CM, Bosworth HB, Pollak KI, Siegler IC, Rimer BK: Relationships among breast cancer perceived absolute risk, comparative risk, and worries. Cancer Epidemiol Biomarkers Prev 2000;9:973–975.

27 Finney Rutten LJ, Gollust SE, Naveed S, Moser RP: Increasing public awareness of direct-to-consumer genetic tests: health care access, internet use, and population density correlates. J Cancer Epidemiol 2012;2012:309109.

28 Mai PL, Vadaparampil ST, Breen N, McNeel TS, Wideroff L, Graubard BI: Awareness of cancer susceptibility genetic testing: the 2000, 2005, and 2010 National Health Interview Surveys. Am J Prev Med 2014;46:440–448.

29 Wang C, O’Neill SM, Rothrock N, Gramling R, Sen A, Acheson LS, Rubinstein WS, Nease DE Jr, Ruffin MT 4th; Family Healthcare Impact Trial (FHITr) group: Comparison of risk perceptions and beliefs across common chronic diseases. Prev Med 2009;48:197–202.

30 Bleiker EM, Esplin MJ, Meiser B, Petersen HV, Patenaude AF: 100 years Lynch syndrome: what have we learned about psychosocial issues? Fam Cancer 2013;12:325–339.

31 Dancyger C, Smith JA, Jacobs C, Wallace M, Michie S: Comparing family members’ motivations and attitudes towards genetic testing for hereditary breast and ovarian cancer: a qualitative analysis. Eur J Hum Genet 2010;18:1289–1295.

32 Dickson MR, Carter CL, Carpenter MJ, McClure RL, McGee DA, Zapka JG, Strange C: Barriers to genetic testing among persons at risk for alpha-1 antitrypsin deficiency. Genet Test 2008;12:501–505.

33 Erskine KE, Hidayatallah NZ, Walsh CA, McDonald TV, Cohen L, Marion RW, Dolan SM: Motivation to pursue genetic testing in individuals with a personal or family history of cardiac events or sudden cardiac death. J Genet Couns 2014;23:849–859.

34 Lemke AA, Bick D, Dimmock D, Simpson P, Veith R: Perspectives of clinical genetics professionals toward genome sequencing and incidental findings: a survey study. Clin Genet 2013;84:230–236.