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Views of Genetics Health Professionals on the Return of Genomic Results

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Abstract

As exome and whole genome sequencing become clinically available, the potential to receive a large number of clinically relevant but incidental results is a significant challenge in the provision of genomic counseling. We conducted three focus groups of a total of 35 individuals who were members of ASHG and/or NSGC, assessing views towards the return of genomic results. Participants stressed that patient autonomy was primary. There was consensus that a mechanism to return results to the healthcare provider, rather than patient, and to streamline integration into the electronic health record would ensure these results had the maximal impact on patient management. All three focus groups agreed that pharmacogenomic results were reasonable to return and that they were not felt to be stigmatizing. With regard to the return of medically relevant results, there was much debate. Participants had difficulty in consistently assigning specific diseases to ‘bins’ that were considered obligatory versus optional for disclosure. Consensus was reached regarding the importance of informed consent and pretest counseling visits to clarify what the return of results process would entail. Evidence based professional guidelines should continue to be developed and regularly revised to assist in consistently and appropriately providing genomic results to patients.

Keywords

Whole genome sequencing; whole exome sequencing; return of results; informed consent; patient autonomy; pretest counseling; professional attitudes

INTRODUCTION

As the costs of sequencing continue to decline, technologies such as whole exome sequencing (WES) and whole genome sequencing (WGS) have received increasing attention for their role in the future of personalized medicine. WGS and WES can be used specifically

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to identify a diagnosis and improve understanding of disease (Bainbridge et al. 2011; Lin et al. 2012; Need et al. 2012; Raffan et al. 2011; Worthey et al. 2011), but may also reveal hundreds of potentially significant genetic variants for each individual (Ashley et al. 2010; Cassa et al. 2012). While largely occurring within the research realm, several clinical laboratories have recently started offering whole exome and genome sequencing for specific indications, such as eliciting the genetic cause of a complex clinical presentation, or to identify risks and diagnoses (Ambry Genetics 2012; Baylor College of Medicine 2012; GeneDx 2012; UCLA Pathology and Laboratory Medicine 2012). In 2010 the first clinically oriented evaluation of an individual patient's whole genome was published, demonstrating the powerful information that can be derived about disease risk and drug response in those who undergo such testing (Ashley et al. 2010). As WES and WGS become increasingly clinically available, the potential to receive a large number of clinically relevant incidental results, including those with potential clinical validity and clinical utility, is a significant challenge in the provision of genomic counseling.

Thus far, the majority of WES and WGS studies have taken place within research settings in a cautious manner around the return of individual research results, particularly with regard to incidental and clinically significant findings. While some groups argue that it is obligatory for researchers to return, or at least offer to return, results that have high analytic and clinical validity or important health implications for the participant (Fabsitz et al. 2010; Wolf et al. 2008), others suggest that it may be permissible to offer results if there is any possibility of clinical utility, and that context is critical (Berg et al. 2011; Beskow and Burke 2010; Wolf et al. 2008). Regardless of the approach taken, many studies have demonstrated that research participants do wish to be informed about genomic research results, especially if they are of clinical significance (Beskow and Burke 2010; Biesecker 2012; Bollinger et al. 2012; Kaufman et al. 2008; Meacham et al. 2010; Meulenkamp et al. 2010; Partridge et al. 2003).

Clinical and research sequencing contexts clearly differ in terms of several key underlying principles, including the general goals and purpose of research versus clinical testing, the nature of the relationship and obligations between a researcher and participant versus a clinician and patient, and the expectations with regard to results delivery and individual benefit (Clayton and McGuire 2012). However, increasing attention to the issue of returning genomic results in research settings has identified several clinically relevant points to consider, for which important ongoing genomics studies have been developed; including the MedSeq project, aimed to create and test methods for integrating WGS into clinical care (MedSeq Project, Genomes2People 2013), and the Electronic Medical Records and Genomics Network, aimed to leverage biorepositories and electronic medical records to research the return of genomic findings in a clinical context (eMERGE 2013). These include: specific findings considered clinically actionable (Fullerton et al. 2012), the identification of large amounts of clinically uncertain results (Fullerton et al. 2012; Ormond et al. 2010), and findings indicative of disease susceptibility in the absence of family or personal history (Biesecker 2012). Several bodies have created recommendations for the return of individual genetic research results (Cassa et al. 2012; Fabsitz et al. 2010), including the proposition that variants should be disclosed to research participants based on validity of

the association, phenotypic severity, improvement with treatment, analytic validity, and participant consent (Cassa et al. 2012).

There are now recently published guidelines for the return of incidental findings from clinical genomic sequencing by the American College of Medical Genetics and Genomics (Green et al. 2013), and groups such as EGAPP are also in the process of developing approaches for categorizing and disclosing such results. While the recent ACMG guidelines provide a starting place and model for handling incidental findings in the clinical genome and exome sequencing settings, the authors acknowledged that there is still insufficient evidence about the benefits, limitations, and costs of disclosing such incidental findings and that ongoing revisions and updates to these guidelines will be necessary to incorporate new findings and data that emerge (Green et al. 2013). Some recently published studies have explored the development of conceptual approaches and lists of results for disclosure in clinical WGS, suggesting the potential tactic of “binning” specific results (Berg et al. 2011; Green et al. 2012). More specifically, Green and colleagues found that while specialists in clinical genetics and/or molecular medicine were fairly concordant in determining which incidental findings were *permissible* to return, further research is needed to explore the underlying reasons for the disagreements observed in disclosing incidental findings and in weighing criteria that influence disclosure decisions (Green et al. 2012), as well as to further determine which incidental findings, if any, are obligatory to return in clinical genome sequencing settings.

The sheer scale of WES and WGS requires careful consideration of the risks and benefits of clinical implementation (Lerner-Ellis 2012). Given the numerous stakeholders involved as this type of testing becomes clinically available, it will be important to determine their perspectives to ultimately develop appropriate guidelines. The goal of this study was to gain understanding of the factors that influence attitudes towards incidental results disclosure in WES and WGS through three focus groups with genetics healthcare professionals, and to determine a means of prioritizing such results as this moves into the clinical realm. This is the first arm of a larger study that will assess the opinions of professionals in numerous medical specialties.

MATERIALS AND METHODS

Study Design and Participants

We conducted a qualitative study to explore views of genetics health professionals toward the return of incidental genomic results. This study was reviewed and approved by the Stanford University Institutional Review Board, and written informed consent was obtained from all 35 participants.

Recruitment

Study participants were recruited by email between September and October of 2011 from lists of attendees at the annual meetings of the American Society of Human Genetics (ASHG) and National Society of Genetic Counselors (NSGC). We enrolled the first 15 individuals who contacted us from each group. Inclusion criteria required board certification

in their respective genetics field. Participants were offered compensation for participation in the form of a \$100 widely redeemable gift card, and a meal if the focus group occurred during a mealtime.

Procedures

In October 2011, each study subject participated in a two-hour focus group conducted at either the International Congress of Human Genetics/ASHG Annual meeting in Montreal, Quebec (1 focus group, 11 participants), or the NSGC Annual Education Conference in San Diego, California (2 focus groups, 12 participants each). Each group utilized a semi-structured focus group guide with a single moderator (KEO). Focus groups were recorded using digital audio recording and were transcribed for analysis.

Focus Group Guide

The focus group guide included open-ended questions and prompts within four major areas for discussion: (1) General views toward the return of incidental WGS results; (2) Disease categories for disclosure, including pharmacogenomic results; (3) Impact of stakeholder preferences; and (4) Questions to assess motivations for participation in the focus group and participant demographics.

Data Analysis

Transcripts were coded and analyzed using a grounded theory approach to identify emergent themes related to the research questions and study aims, utilizing NVivo 9.0 software. Two investigators (MG, MW) validated the transcripts with recordings and notes from the sessions. The focus group guide categories were used as a framework to develop primary codes, and after initial reviews of the transcripts, secondary codes and sub codes were generated. Study investigators compared the coded transcripts, modified codes as needed and developed rules and definitions to ensure consistency. Codes from this finalized coding list were then applied to each of the three focus group transcripts by two study investigators (M.G. and M.W.); 33% of transcripts were chosen at random to be verified for consistency. Line-by-line codes were compared, and instances of agreement were counted, as were total coding decisions by each coder. An initial coefficient reliability of 90% was achieved and discrepancies were resolved before coding continued.

RESULTS

Participants

Participants had a range of clinical and/or research experiences, and many were involved in multiple settings. The majority of participants were involved in returning genetic test results to patients, and several were working in settings already conducting research-based WES or WGS. The 11 participants in the ASHG focus group consisted of genetic counselors (5); physicians of various specialties involved in genetics research (2); clinical geneticists (2); and basic scientists in genetic research laboratories (who currently have limited contact with WGS participants) (2). The 24 participants in the NSGC focus groups consisted of genetic counselors, involved in an overlapping range of clinical (20), laboratory (2), industry (2) and research (6) settings.

The majority of participants described motivations for participation in the focus group as related to the perceived importance of WGS, the desire to discuss this form of testing and its related implications with colleagues, and the need to convey the complex nature of this type of testing to patients and the general public.

Qualitative analysis identified the following important themes related to the disclosure of incidental results from WGS or WES results. Representative quotations from the focus groups are included.

Informed Consent and Patient Autonomy

In general, most focus groups participants agreed that patient autonomy and values should be the primary guide in deciding what results to disclose, and that the content of pretest counseling and informed consent with the patient should direct what information is ultimately disclosed. The few participants who disagreed on this point were concerned about finding medically actionable variants in patients who declined such incidental results; some felt patient preference should be respected and others felt that there might be conditions that health care providers were obligated to report. One participant suggested the need for determining “core components” of such pre-test counseling, and developing guidelines to help standardize the components of such counseling.

“...What are the categories that we want to provide people- you know, the opt-in, opt-out information [...] and then similarly a standardized and studied process for when we come back to people after sequencing. Whether it’s right now or in 5 years or in 10 years, how do we revisit those conversations and what are the considerations we need to review with people.” (ASHG focus group participant)

While the patient preferences expressed in pretest counseling were seen as critical to guide the disclosure of results, many study participants felt that it needs to be seen as a flexible and iterative process. Many discussed the need for a ‘dynamic informed consent’ and an ‘unlocking results’ process to take into account not only the changing interpretations of the genome, but also the changing values and contexts of patients over time. This ‘unlocking’ concept was applied in two apparently distinctive ways in the different focus groups. Some referred to the concept that the data is stored and interrogated regularly, and that the knowledge and our interpretation of it will change over time. A few participants described a process where as new results become available or are discovered to be clinically significant, these are “unlocked” to the participant. Other participants referenced the concept of unlocking in terms of releasing genetic results derived from WGS over time and at ages when a particular medical action or intervention might be relevant or applicable, as was discussed above. For example, a model in which patients would follow up with their genetics professional (an individual specifically trained and/or board certified in clinical genetics, such as a genetic counselor, geneticist, or genetic nurse) over time to incorporate the changing genome interpretations and discuss relevant findings at the appropriate time. This resonated with several participants as a potential approach to organize and manage the vast amounts of data derived from WGS/WES.

“What I need today from my genome sequencing isn’t what I’m gonna need 5 years from now. And I think about the preventive you know timeline that we look at in the

doctor's office every time you go to see your OB-GYN. When I'm 20 to 25, I need to have my cholesterol screened once every 5 years. I need to have, so having something like that in the whole genome, what do I need to unlock and what do I need to, do I need to find out about this now? [...] What do I want, so some concept like that I think needs to be flushed out." (NSGC focus group participant)

However, there were concerns about the liability and risks this could pose to patients. For instance, should a patient be lost to follow-up, misinterpret their results, or have the ability to incorporate risks for late-onset conditions or "later actionable" findings into their lifestyle and take preventative measures, then the idea of unlocking results over time becomes problematic. Several individuals expressed concerns about blinding specific information, fearing that patients may not truly understand the distinction between a negative result and a merely unanalyzed result.

Challenges in the delivery of genomic medicine

Focus group participants identified several stakeholder groups including healthcare providers, genetics experts (which include, but are not limited to clinical genetics professionals), researchers, laboratories, and patients / research participants who have varying levels of rights and responsibilities toward the return of genomic results. The specific roles discussed included interpretation of the genome, disclosure of results, reinterpretation of the genome over time and staying current with new developments, access, data storage, education, and others. There was little consensus about which stakeholders should hold responsibility for the various roles, and much of the discussion in all focus groups raised questions and discussed the various pros and cons of different approaches. Some participants felt the onus for controlling who orders tests, interpretation, and regular interrogation of the genome should fall on the laboratory. Others felt this was impractical and that either the patient (few participants) or healthcare provider (most participants) should take responsibility for his or her results, what is disclosed, and when. It was seen as different for a clinician to receive the entire genome sequence for a patient and needing to make decisions around what and when to clinically disclose, versus receiving a filtered result from the laboratory in relation to the patient's preferences.

Participants also struggled with the question of whether healthcare providers and clinicians would have the resources and/or knowledge to conduct pre-test informed consent, properly order and deliver results of genomic sequencing; some suggested regulation of who can order and interpret genomic sequencing. There were also concerns about the feasibility of storing the entire genome in the electronic medical record and utilizing technological tools to interpret and analyze the data over time. Several individuals discussed the importance of necessary clinical providers having access to this information (particularly with regard to pharmacogenetic data) through EMRs; but questions remained regarding who exactly can access this data, and how it will be protected.

"I think one of my biggest questions is you know whether you know we are doing this in a non-blinded fashion, whose responsibility is it to go through every bit of information that we have, and whose responsibility is it to then keep up to speed with new developments. So we found a variant today, we didn't know what it was."

In two years we know it's associated with brain cancer. You know is it the patient's responsibility to keep up with that information? Is it their primary care physician? Is it the ordering physician? You know I don't, those are things we're gonna have to figure out so that we don't have all this really powerful information and it gets lost in the shuffle after that initial question that prompted the testing was answered.” (NSGC focus group participant)

When asked to what degree, if any, an individual research subject's and ultimately, patient, preferences should determine which results get reported, all groups placed the responsibility on the patient when determining which incidental results to return, how to return them, and when; this was consistent with the focus on patient autonomy. A few participants proposed a system where the patient is also responsible for follow-up and triaging the results derived from their genome results. Others voiced concerns about patients who may not have the proper knowledge to know what questions to ask of their genomes, and the disadvantages or risks this could pose. Several individuals raised the issue of whether an individual or family was 'the patient'.

Categorizing Incidental Results

Participants frequently mentioned the need for the incorporation of a multidisciplinary and long-term approach when determining what types of incidental results to return. All three groups suggested the idea of creating multidisciplinary expert panels, drawing from stakeholder professional groups, to determine criteria and guidelines for what types and categories of results are disclosed.

When asked about which specific conditions and findings, if any, would be obligatory to disclose after WGS/WES, participants described many conceptual categories of results and factors that influenced their opinions. These included: clinically actionable results; penetrance; disease severity; characteristics of the genetic variant (including certainty about pathogenicity); treatment options; age of onset of the condition; incidence; and stigma. Actionability was the most frequently discussed category in all groups but there was a lack of consensus around what necessarily constitutes “clinically actionable.” Some individuals included lifestyle changes and nonmedical interventions in this category, while others limited it to a medical treatment or intervention option, and efficacy was an important factor.

Participants discussed the potential approach of ‘binning’, where healthcare providers would place conditions and/or specific genetic results into categories (“bins”) and the patient would subsequently consent to those larger categories (rather than individual conditions).

“I mean could you present categories to somebody and say, ‘I only want to know about something that is related to my indication, or I want to know about all carrier status.... I want to know about things that might have an onset before I'm 30, or I want to know about everything.’ And we would have the responsibility of putting each disease in buckets... And the patient would have to consent to huge chunks.” (NSGC focus group participant)

Despite consensus on the need for ‘binning,’ participants found it difficult to agree on the placement of specific disorders into categories for disclosure. Several participants suggested

that WGS/WES in a healthy population versus for other indications might influence how such ‘bins’ are sorted. For example, the example of *BRCA* mutations was discussed frequently, without consensus. While some participants felt that the known *BRCA* mutations would require obligatory disclosure, citing clinical actions and penetrance, others were less sure and discussed respecting patient decisions and the fact that *BRCA* mutations confer a predisposition to cancer, rather than a definitive diagnosis. Particularly with regard to the cancer predisposition syndromes, many focus group participants described mixed feelings; on the one hand, they felt required to adhere to the consent and research protocol, but on the other, they felt somewhat obligated to disclose this type of clinically actionable result. Several participants proposed a potential strategy that emphasizes the conditions or types of genetic results that would *not be* included in the buckets, and therefore not reported. Groups stressed transparency regarding what is being tested for, what is included in each bin, and how the bins are developed. One NSGC focus group seemed to approach consensus regarding some conditions within the category of predictive testing that might require disclosure if discovered.

“I think that the two conditions that I’ve heard the most from the group about things that are the most anxiety-producing for us if it was on our desk and we would be really inclined to share with the patient are [...] ones that will have a risk of death as a minor. So childhood cancers and sudden death like cardiomyopathy that came up as well.” (NSGC focus group participant)

Finally, two specific categories of testing were explicitly discussed: carrier testing and pharmacogenomic results. Participants reported comfort disclosing carrier results to adults, often referencing the fact there are already guidelines or testing panels, such as in Ashkenazi Jewish carrier screening, available. Concerns were raised, however, about disclosing these results in children. Participants generally agreed that pharmacogenomic results have low harm, potential benefit, and do not deliver a diagnosis that could come with stigma. Many discussed the idea of disclosing pharmacogenomic information as more ‘common sense,’ because doctors already take risks with drugs and dose titration. There was not consensus, however, on how best to provide and utilize pharmacogenomic data. Two recurring issues arose in the focus groups surrounding pharmacogenomics: first, there were concerns about losing the power of this information due to a lack of portability or a mechanism to stay current with changing results; and second, participants questioned the ability of pharmacogenomic information to be successfully integrated into universal clinical practice. Several individuals felt that this information should be directed primarily to physicians, rather than patients, for future use; some expressed the need for an electronic health record system to prompt health care providers when a particular pharmacogenomic result becomes relevant.

DISCUSSION

We found diverse views among genetics professionals surrounding the return of incidental findings from WGS and WES. Our study is among the first to explore stakeholder views influencing incidental results disclosure decisions as sequencing moves into the clinical

realm, particularly in light of the release of the first published guidelines to address these critical issues in the clinical setting (Green et al. 2013).

The theme of challenges surrounding WES/WGS – particularly with regard to scale, potential for misinterpretation, and the concept of a reasonable limit – came up repeatedly in our focus groups, consistent with previous studies (Biesecker 2012; Kohane et al. 2012; Lerner-Ellis 2012; Ormond et al. 2010). Informed consent and pretest counseling were seen as critical but challenging to achieve, balancing a need for a dynamic consent process to take into account both changing genome interpretations and patient values over time, the ability to achieve appropriate consent, and desire to limit who can order such tests. Numerous logistical and infrastructural challenges were raised, particularly in relation to these issues of interpreting (and reinterpreting) data over time and incorporating updated patient preferences for result return and future follow up.

Participants often brought up the different settings – research and clinical – in thinking about return of incidental findings from WGS or WES, and the similarities and differences that may occur between these settings. In our study, testing context played a significant role in how categories of incidental results are divided and ultimately disclosed. When describing the elements that influence the context of testing, participants typically described factors related to the patient his or herself, including motivation for testing and ethnic, cultural or emotional issues; as well as factors related to logistical or administrative issues such as testing indication, the research protocol or consent form.

While the concept of bucketed or binned categories arose frequently as a strategy for organizing and managing the large number of potential findings (Berg et al. 2011), participants had difficulty reaching consensus on defining the buckets and which conditions they would comprise, even when applying existing models, such as a newborn screening model. The most frequently discussed criteria for disclosure included clinically actionable findings, pharmacogenomic results, carrier testing, and predictive testing for both cancer predisposition syndromes and neurodegenerative conditions. Pharmacogenomics and carrier status were among those categories with highest consensus among our focus group participants (which are not included as part of the initial ACMG (Green et al., 2013) recommended gene list), but participants disagreed on who would be responsible for updating and communicating such findings. While this seems consistent with other studies that focus on healthcare provider attitudes toward pharmacogenomic testing in general, and the promise of WGS and WES in identifying individuals at-risk for adverse drug events (Berg et al. 2011; Fargher et al. 2007); it contrasts with the results of a recent study which assessed specific conditions and types of variants that genetic specialists recommended for return to the patient's ordering physician upon incidental discovery (Green et al. 2012), as well as with the recent ACMG recommendations on disclosure of incidental findings (Green et al., 2013). Whereas all sixteen genetic specialists in that study agreed to return incidental results concerning various cancer predisposition syndromes, and the ACMG recommendations include 57 genes that include but are not limited to cancer predisposition, our focus group participants did not unanimously agree on disclosing such conditions, particularly in the absence of pre-testing consent to receive such results. This comparison suggests that such recommendations do not represent traditional, albeit conservative,

practice, and that incorporation of these recommendations into clinical practice should be studied to assess the impact for clinicians and patients.

Discussions around responsibility and obligation proved to be informative, both in identifying the major stakeholders who will be involved in these decisions and in terms of understanding more of the complexity around disclosure of incidental findings in WGS or WES. Participants identified healthcare providers and genetics experts, testing laboratories, and patients as being the major players. However, there was little consensus regarding who should be most responsible for long-term follow up. Focus groups appeared to agree on the important role of the patients and patient autonomy, and this is consistent with the recurrent theme of informed consent and developing appropriate criteria for pretest counseling. Importantly, this theme of patient autonomy as paramount was recently echoed by lay public focus groups in a study that compared public and genetic professionals views of incidental findings; these lay groups expressed concern about paternalism and discussed that patient choice (rather than clinical relevance) should determine criterion for disclosure (Townsend et al. 2012).

Study Limitations

As a small study, comprising 35 individuals attending the annual conferences for both ASHG and NSGC, it is possible that the participants are not fully representative of their respective professional groups in terms of their background and views on this subject. The individuals who opted to participate in this study may have a particular interest in whole genome sequencing and have strong opinions around incidental results disclosure. The majority of participants in this study were also genetic counselors, who may hold different views than other genetic health professionals. As this project is part of an ongoing study on healthcare provider views towards the return of genomic results, the results of this study are not intended to be universally generalizable. It will be important to determine opinions of other medical specialists with regard to this topic, and to work toward methods for prioritization of exome and whole genome sequencing results. Future research should also seek to explore additional stakeholder opinions, specifically with regard to other medical specialists and research participants or patients who have received incidental findings in other settings. We aim to use the knowledge gained from this and related studies, as well as recently published guidelines, to serve as a baseline to assess the views and other considerations for return of incidental findings in various medical specialties in a more structured manner.

CONCLUSIONS

Our findings highlight the complexities inherent in the task of developing guidelines or standards to guide the return of incidental genomic results. Participants in these focus groups placed a high priority on patient/subject autonomy in determining return of incidental results from sequencing. While there was a general consensus that ‘binning’ could be helpful in managing the large volume of results from these tests, participants were reluctant to place specific conditions in bins for disclosure. Challenges such as dealing with the shifting nature of results and interpretations arose frequently, and the development of a dynamic informed

consent to enable flexibility over time was proposed. While consensus was not reached about whether and what specific results to disclose, emerging themes seem to suggest that researchers and clinicians have an obligation to be involved in the evolution of strategies for approaching categorization and prioritization around incidental findings derived from whole genome and whole exome sequencing. We would recommend that further discussions take place that aim to develop consistent guidelines amongst professional organizations, and include diverse healthcare providers in the decision-making process. Additionally, we recommend further and ongoing development of current guidelines in this area, as new data will inevitably emerge and there are many circumstances not addressed by any guidelines in clinical settings to date, such as clinical sequencing of healthy individuals, legal and liability implications of returning or withholding sequencing results, elements of genomic sequencing pretest counseling and informed consent, and others (Green et al. 2013).

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References

- Ambry Genetics. 2012. Retrieved March 28, 2012 from: <http://www.ambrygen.com/genomic-services/exome-sequencing>
- Ashley EA, Butte AJ, Wheeler MT, et al. Clinical assessment incorporating a personal genome. *The Lancet*. 2010; 375:1525–1535.
- Bainbridge MN, Wisniewski W, Murdock DR, et al. Whole-Genome Sequencing for Optimized Patient Management. *Science Translational Medicine*. 2011; 3:87re3.10.1126/scitranslmed.3002243
- Baylor College of Medicine, Whole Genome Laboratory. 2012. Retrieved March 28, 2012 from: <https://www.bcm.edu/geneticlabs/index.cfm?PMID=21319>
- Berg JS, Khoury MJ, Evans JP. Deploying whole genome sequencing in clinical practice and public health: Meeting the challenge one bin at a time. *Genetics in Medicine*. 2011; 13:499–504. [PubMed: 21558861]
- Beskow LM, Burke W. Offering Individual Genetic Research Results: Context Matters. *Science Translational Medicine*. 2010; 2:38cm20.10.1126/scitranslmed.3000952
- Biesecker LG. Opportunities and challenges for the integration of massively parallel genomic sequencing into clinical practice: lessons from the ClinSeq project. *Genetics in Medicine*. 2012; 14:393–398. [PubMed: 22344227]
- Bollinger JM, Scott J, Dvoskin R, Kaufman D. Public preferences regarding the return of individual genetic research results: findings from a qualitative focus group study. *Genetics in Medicine*. 2012; 14:451–457. [PubMed: 22402755]
- Cassa CA, Savage SK, Taylor PL, Green RC, McGuire AL, Mandl KD. Disclosing pathogenic genetic variants to research participants: quantifying an emerging ethical responsibility. *Genome Research*. 2012; 22:421–428. [PubMed: 22147367]
- Clayton EW, McGuire AL. The legal risks of returning results of genomic research. *Genetics in Medicine*. 2012; 14:473–477. [PubMed: 22323070]
- The eMERGE Network. 2013. Retrieved April 1, 2013 from: <http://emerge.mc.vanderbilt.edu>
- Fabsitz RR, McGuire A, Sharp RR, et al. National Heart, Lung, and Blood Institute working group. Ethical and practical guidelines for reporting genetic research results to study participants: updated

- guidelines from a National Heart, Lung, and Blood Institute working group. *Circulation Cardiovascular Genetics*. 2010; 3:574–580. [PubMed: 21156933]
- Fargher EA, Eddy C, Newman W, et al. Patients' and healthcare professionals' views on pharmacogenetic testing and its future delivery in the NHS. *Pharmacogenomics*. 2007; 8:1511–1519. [PubMed: 18034616]
- Fullerton SM, Wolf WA, Brothers KB, et al. Return of individual research results from genome-wide association studies: experience of the Electronic Medical Records and Genomics (eMERGE) Network. *Genetics in Medicine*. 2012; 14:424–431. [PubMed: 22361898]
- GeneDx. 2012. Retrieved June 1, 2012 from: <http://www.genedx.com/test-catalog/xomedx/>
- Green RC, Berg JS, Berry GT, et al. Exploring concordance and discordance for return of incidental findings from clinical sequencing. *Genetics in Medicine*. 2012; 14:405–410. [PubMed: 22422049]
- Green, RC.; Berg, JS.; Grody, WW., et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. 2013. Retrieved April 2, 2013 from: <http://www.acmg.net/docs/ACMG_Releases_Highly-Anticipated_Recommendations_on_Incidental_Findings_in_Clinical_Exome_and_Genome_Sequencing>
<http://www.torion.com/products/24>
- Kaufman D, Murphy J, Scott J, Hudson K. Subjects matter: a survey of public opinions about a large genetic cohort study. *Genetics in Medicine*. 2008; 10:831–839. [PubMed: 19011407]
- Kohane IS, Hsing M, Kong SW. Taxonomizing, sizing, and overcoming the incidentalome. *Genetics in Medicine*. 2012; 14:399–404. [PubMed: 22323072]
- Lerner-Ellis J. The clinical implementation of whole genome sequencing: a conversation with seven scientific experts. *Journal of Inherited Metabolic Disease*. 2012; 35:689–693. [PubMed: 22403015]
- Lin Z, Chen Q, Lee M, et al. Exome Sequencing Reveals Mutations in TRPV3 as a Cause of Olmsted Syndrome. *American Journal of Human Genetics*. 2012; 90:558–564. [PubMed: 22405088]
- Meacham MC, Starks H, Burke W, Edwards K. Researcher perspectives on disclosure of incidental findings in genetic research. *Journal of Empirical Research on Human Research Ethics*. 2010; 5:31–41. [PubMed: 20831419]
- The MedSeq Project, Genomes2People. 2013. Retrieved April 1, 2013 from: <http://www.genomes2people.org/g2p/medseq/>
- Meulenkamp TM, Gevers SK, Bovenberg JA, Koppelman GH, van Hylckama Vlieg A, Smets EMA. Communication of biobanks' research results: What do (potential) participants want? *American Journal of Medical Genetics Part A*. 2010; 152:2482–2492. [PubMed: 20799322]
- Need AC, Shashi V, Hitomi Y, et al. Clinical application of exome sequencing in undiagnosed genetic conditions. *Journal of Medical Genetics*. 2012; 49:353–361. [PubMed: 22581936]
- Ormond KE, Wheeler MT, Hudgins L, et al. Challenges in the clinical application of whole- genome sequencing. *Lancet*. 2010; 375:1749–1751. [PubMed: 20434765]
- Partridge AH, Burstein HJ, Gelman RS, Marcom PK, Winer EP. Do patients participating in clinical trials want to know study results? *Journal of the National Cancer Institute*. 2003; 95:491–492. [PubMed: 12644548]
- Raffan E, Hurst LA, Al Turki S, et al. Early diagnosis of Werner's syndrome using exome- wide sequencing in a single, atypical patient. *Frontiers in Endocrinology*. 2011; 210.3389/fendo.2011.00008
- Townsend A, Adam S, Birch PH, et al. "I want to know what's in Pandora's Box": Comparing stakeholder perspectives on incidental findings in clinical whole genomic sequencing. *American Journal of Medical Genetics Part A*. 2012; 158:2519–25. [PubMed: 22903777]
- UCLA Pathology and Laboratory Medicine. 2012. Retrieved June 1, 2012 from: <http://pathology.ucla.edu/body.cfm?id=292>
- Wolf SM, Lawrenz FP, Nelson CA, et al. Managing Incidental Findings in Human Subjects Research: Analysis and Recommendations. *Journal of Law, Medicine & Ethics*. 2008; 36:219–248.
- Worthey EA, Mayer AN, Syverson GD, et al. Making a definitive diagnosis: Successful clinical application of whole exome sequencing in a child with intractable inflammatory bowel disease. *Genetics in Medicine*. 2011; 13:255–262. [PubMed: 21173700]