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Genomic sequencing for psychiatric disorders: Promise and challenge

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Abstract

The integration of whole genome and whole exome sequencing (WGS/WES) into medicine introduces a new paradigm in genetic testing. The promise of sequencing will ultimately reshape psychiatry. In the meantime, this revolution will present challenges as researchers and clinicians interpret sequence data and make decisions about if, when, and how data should be offered. Individuals may request sequence data to better understand illness etiology, prognosis, and/or treatment response; to clarify their own disease risk; or out of curiosity. This commentary on the ethics of returning WGS/WES data describes the uniqueness of the data as a dynamic health resource; the importance of understanding participant motivations; determinations of personal utility; and potential effects of WGS/WES on self-concept and wellbeing. Clinicians and patients have navigated prior "revolutionary" genetic technologies while managing ethical challenges. Research into participant/patient perceptions, preferences and outcomes will realize areas of caution and prepare for integration into clinical care.

Keywords

sequencing psychiatric genetics ethics

Introduction

The integration of whole exome and whole genome sequencing (WES/WGS) into medicine (including psychiatric medicine) introduces a new paradigm in genetic testing. This revolution will lead to an era of personalized medicine that will redefine disease groupings, allow targeting of therapies, and illuminate complex etiologies (Green et al., 2012). The availability of sequencing will lead to widespread use throughout the health care sector and beyond. Advances will be achieved in refining frequency and penetrance of variants, and clarifying relationships between variants and disease risk based on gene/environment interplay. In psychiatry, these outcomes are anticipated to result in etiologically-informed diagnostic categories, identification of drug sensitivity, targets for rational therapies, and more accurate risk prediction. The promise of sequencing will take decades to be fully realized, but will ultimately reshape the practice of psychiatry. In the meantime, this revolution will present a plethora of challenges as researchers and clinicians interpret sequence data and apply it to clinical care.

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Statement of Interest
None

The integration of WES/WGS into research and clinical care has been facilitated by a steep reduction in cost; conducting a sequence analysis is often less expensive than performing a series of more traditional genetic interrogations. Representatives of third party payers are speaking out about the potential cost effectiveness of forgoing genetic tests in favor of whole genome or whole exome sequencing (Genetic Testing and Data Management Summit, Genetic Alliance, March 12, 2012). This practice is likely to become widespread as the costs of WGS dramatically decrease in the near term. WES/WGS are currently offered as targeted clinical tests, primarily to identify the genetic origins of rare undiagnosed conditions (companies offering such testing include Ambry Genetics, Baylor College of Medicine Laboratories, GENDIA, and GeneDx.) For example, a patient with features of 22q-, velo-cardio-facial syndrome (which includes increased risk for a range of mood and psychotic disorders) with a negative microarray test result may be a candidate for WES to identify the cause of the phenotype.

In the near future, WES/WGS will be used clinically to identify known and novel risk factors for psychiatric disease, along with other common conditions. Prior to such direct clinical use, there may be an indirect path through which WGS data are used to inform about risk for/cause of psychiatric diagnoses; i.e., whole genome sequencing may be done to identify a cause for a particular disorder, and the patient may express interest in having access to more of the sequencing data. Even if the intent of the sequencing was not to inform about psychiatric illness, we can anticipate that individuals with major psychiatric disorders may want to have access to the data (over time) to better understand the cause for their illness, prognosis, and/or treatment response; individuals at risk based on their family history may be interested in receiving data that clarifies their own risk; and individuals in the general public may have interest in predictive information simply based on the prevalence of psychiatric disorders.

The return of individual WES/WGS data will likely occur primarily within research endeavors before moving to widespread use in a clinical setting. As such, our commentary on the ethics of returning sequencing data is focused on research use, although many of the issues raised will also prevail in clinical use. A majority of the ethical issues arising from sequencing are not novel. Clinicians and patients have successfully navigated prior “revolutionary” genetic technologies into practice while largely managing the accompanying ethical challenges. Those lessons learned can be applied to this latest revolution, and there is every reason to expect the health care community to adapt to meet the new challenges. Though the scope and scale of the benefits are expected to greatly exceed that of any prior genetic technology, research in the meantime will help realize areas of caution and prepare us for the onslaught of new information.

Use of WES/WGS in Clinical Research

Whole exome and whole genome sequencing are currently used in research settings with indications as wide as diagnosing individuals with rare, unexplained disorders (Need et al., 2012); identifying genetic contributions to genetic syndromes (Montenegro et al., 2011; Solomon et al., 2012); and investigating the genetic contributions of complex disorders, including psychiatric disease (O’Roak et al., 2011; Xu et al., 2011). A number of studies are evaluating participants’ interest in and response to data generated from WGS/WES, including the NIH Return of Results Consortium (http://www.genome.gov/27545526) and the National Human Genome Research Institute’s ClinSeq™ project, which is investigating individual choice about receiving genomic information back from sequencing (Biesecker, 2012; Facio et al., 2011). Included in these studies are questions related to how to return individual results and which results to return. Answers to these questions are informed by bioinformatics, data annotation, and definitions of clinical and personal utility.

Investigators in psychiatric genetics who are using WES/WGS to identify predictive genetic factors and better understand gene/environment interaction are facing complex questions about when and how to return results to research participants. To our knowledge, though several research teams are considering the return of data related to psychiatric phenotypes within a WGS/WES study, no team has yet undertaken this effort.

In most cases, research participants undergoing WES/WGS are told that they will receive only results that are deemed "medically actionable." For the foreseeable future, few sequence data related to psychiatric disorders will be medically actionable, except data that inform treatment decisions. While participants' questions about cause and recurrence (i.e., "why me, and will it happen again in my family?") may be the most important to research participants, such data will be uncertain. Based on surveys and interview studies, there is good reason to expect that individuals with psychiatric disorders and their family members (Trippitelli et al., 1998) (Austin et al., 2006; DeLisi and Bertisch, 2006; Laegsgaard et al., 2009; Meiser et al., 2008; Meiser et al., 2005b; Potokar et al., 2011) and some members of the general public (Wilde et al., 2011) have interest in the genetic data related to cause and risk for psychiatric disorders.

Ethical Issues

As WES/WGS come into use, they raise a number of pragmatic and ethical issues. There is no standard model or guidelines for consenting people to participate in WES/WGS studies or for returning results. We briefly describe points to consider about return of sequence results about psychiatric risk and causation in clinical research on:

1. Sequence data as a dynamic health resource;
2. Participant motivations; and
3. Personal utility

1. WES/WGS data as a dynamic health resource

Arguably, the most remarkable characteristics of WES/WGS pertain to the volume and scope of results. Rather than a single test result that would arise from traditional genetic testing, the output of WES/WGS been described as a resource (Biesecker, 2012) that cannot initially be fully interpreted, but can be re-annotated and referenced over time. While obtaining sequencing data is becoming more commonplace and cost-effective, the interpretation of the output will continue to be time intensive and challenging.

WES/WGS studies are thus longitudinal efforts to curate information to refine risks. Consent to participate in WES/WGS should include the longitudinal nature of the interrogation, making clear the agreed-upon responsibilities of the investigator and the participant for re-contact and follow up (Facio, 2012). Even if the intent of the sequencing is to identify risk factors for psychiatric disease (or any other specific disorder), secondary findings will arise —that is, results that may have associated health risks but are not related to the primary reason the sequencing was performed. When consenting participants to these studies, researchers need to discuss the likelihood of secondary findings and how return of these results will be handled. Experts concur that the potential for secondary findings cannot simply be overlooked by researchers in preference for identification of genes related to the primary disease(s) of interest (Wolf et al., 2008). Researchers will be expected to communicate to participants about research findings related to psychiatric disease, as well as offer "medically actionable" results to individuals. Their participation in studies interrogating genetic contributions to psychiatric disease may include an expectation and even an enthusiasm for learning secondary findings. However, participants eager to learn

about the contributions of their family history (i.e., genetic predisposition) to psychiatric illness may be unprepared to learn, for example, that they carry a mutation in *BRCA1* that places them at significant increased risk for developing breast and ovarian cancer. While the implications of certain results will be relatively straightforward, like the *BRCA1* example, others will be less so. When returned to participants for clinical use, findings must be validated in a CLIA approved laboratory.

For coming decades, researchers and clinicians will have to manage un-interpretable findings and layers of uncertainty as risk estimates are honed. An important aspect of consenting to these studies is an appreciation for the degree of uncertainty. More than ever before, it is vital that researchers (and later, clinicians) identify novel and cost-effective methods of engaging participants or patients in ongoing decision making and support around each persons' WGS/WES resource.

2. Participant Motivations

Given that many WES/WGS studies involve participant choice and decision making about what information to receive, it becomes vital to understand participants' expectations for and motivations to receive individual results. The motivations of study participants (and later consumers) are likely to include (but exceed) the motivations found in traditional genetic testing: seeking a diagnosis and understanding cause.

There are preliminary data available about the motivations of largely healthy individuals to receive data from WES. Participants in the ClinSeq™ study cited altruism and an interest in learning about genetic factors that contribute to overall health (Facio et al., 2011). However, there are no data available on motivations to receive information about risk for a psychiatric outcome—whether from affected individuals, unaffected relatives, or healthy individuals with no family history. Motivations that we can anticipate are described below; together they highlight the importance of effective education and counseling.

a. **Understanding one's own diagnosis and history.** Affected individuals may be motivated to seek genomic data to enhance their acceptance of and adaptation to the diagnosis, further their understanding of the likely course of illness and/or risk for comorbid disorders, and inform their treatment choices. It is unknown how participants may gauge their own behavior in the context of the findings, and how they may respond if their symptoms do not "match" their expected phenotype or disease course based on the genomics data.

b. **Risk assessment for at-risk relatives**. Several studies have reported a strong interest among individuals with psychiatric disorders to use genetic technologies to refine risk for psychiatric disorders in the family (Laegsgaard et al., 2009; Potokar et al., 2011). In a qualitative interview study (Peay et al., 2009), the majority of participants with bipolar disorder and unaffected siblings spoke of a burdensome family vulnerability; i.e., living under the specter of mental illness combined with the risk for mental illness in relatives (Peay et al., 2009). The desire to end the illness cycle might be a strong motivating factor for patients and relatives to seek out genomic data—but once participants receive such information, it is not clear how they will use it.

   The high illness burden and motivation to end the cycle is likely to affect how participants interpret WGS information. These factors are exacerbated by the fact that few interventions have been shown to reduce the risk for major psychiatric disorders (Bunnik et al., 2012), and those that exist are not often available to at-risk offspring of affected adults (Yuh et al., 2006), which limits the "medical actionability" of the data. In addition, a "negative" finding does not mean that

unaffected individuals are at no risk, or even have less than the a priori risk based on family history.

c. Reduce blame about illness in family

In an interview study of individuals with bipolar disorder and close relatives, Meiser et al. (2005) found that most participants reported that genetic explanations of bipolar disorder were helpful in reducing personal and parental blame(Meiser et al., 2005a). Participants may be motivated to use WGS data to manage guilt and blame in the family, by attributing causation to an external biological factor rather than poor environment or personal failure.

d. Curiosity

There will undoubtedly be healthy individuals pursuing their genome sequence to learn about a general set of potential health risks. It is unclear how often they may be curious about their own risks for psychiatric illness, or risk for their relatives. For many people, this may be an unconsidered aspect of the data that could lead to a plethora of questions and concerns.

Understanding and responding to motivations requires questioning, education, and counseling. Prior to WGS, researchers should explore with potential participants what may be unrealistic about their expectations. Researchers should appreciate that the knowledge that participants gain may foster improved coping and perceptions of control, and thus participants may receive psychological benefit from the receipt of the genomic data even in the absence of any direct health effect.

3. Personal utility

Given the evolving nature of WES/WGS, the clinical utility will take time to be established. Genetically-based technologies have traditionally been evaluated by experts (clinicians, ethicists, and scientists) to determine clinical utility. This determination is based on whether the test can accurately measure the specific genetic factor that it is supposed to measure (analytic validity); whether the gene variant causes or predisposes to the disease outcome or trait (clinical validity); and whether the test result matters—for example, is there something that can be done. It is most likely that clinical utility will first be described for WES/WGS that identifies rare mutations for previously undiagnosed conditions.

The clinical utility for psychiatric disease risk is futuristic. However, early studies of WES/WGS demonstrate that early adopters of this technology see beyond the notion of clinical utility, valuing the information regardless of its practical medical utility (Facio et al., 2011; Facio, 2012). Some scholars and investigators have expanded their notions about the value of information to research participants to include personal utility (Kohane and Taylor, 2010; Ravitsky and Wilfond, 2006). Reasons early research participants cite for valuing the information include the potential for lifestyle changes, having information to pass to their relatives, and because having information, even that which cannot currently be interpreted, is desirable (Facio, 2012). These findings suggest that participants may see personal utility in WES/WGS information beyond what is perceived by the investigators (Kohane and Taylor, 2010). This is consistent with data on genetic testing for disorders that are not medically actionable (i.e., no interventions exist). For example, individuals who underwent testing for Huntington's disease, for which there are no effective interventions, described motivations that include reducing uncertainty as well as making lifestyle and reproductive choices (Decruyenaere et al., 2003).

Few authors have suggested concrete, practical guidance to support researchers and clinicians as they attempt to manage the education and informed consent process that is

required to facilitate individual decisions of personal utility. This is an important area of research, and one that would benefit from the engagement of mental health professionals who have experience helping clients manage uncertainty and complex decision-making.

Conclusions

The promise of sequencing is anticipated to play a role in reshaping the practice of psychiatry, resulting in etiologically-informed diagnostic categories, identification of drug sensitivity, targets for rational therapies, and more accurate risk prediction. However, the genomics field is moving beyond traditional genetic testing at a pace for which the community is ill prepared. A new technology as powerful as WGS is likely to be disruptive —especially given the dynamic nature of the results. While early data suggest that individuals who seek out the technology anticipate and find personal utility in the results, providers must expect to help patients make informed choices about personal acceptability, make meaning of data from their "genomic resource," manage uncertainty, and anticipate new data interpretation that will follow.

Current and future efforts to understand research participants' motivations, choices, and reactions to sequencing data will inform the transition of WGS from use primarily in the research setting to widespread clinical adoption. In the meantime, researchers and clinicians should explore participant/patient motivations, and when necessary moderate their expectations. Overblown expectations may lead to disillusionment. At this early stage in the technology, it is a constant challenge to balance the promise of the technology with the overwhelming nature of its implementation. Efforts to educate researchers, providers, and healthcare systems may help reduce disillusionment and allow participants and patients to have better access to knowledge and support, with improved participant/patient wellbeing as the primary driving outcome.

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Table 1

Distinctions between techniques that examine genetic material

	"Traditional" genetic testing (individual tests or panels of individual tests)	**Whole genome sequencing**	**Whole exome sequencing**
Description	Evaluates one area or a defined number of areas of the genome for a particular outcome that is hypothesized based on symptoms and/or family history	Maps the organism's entire genetic code with no predetermined target	Maps the organism's genetic code found within the exons with no predetermined target
Typical use of results	Confirm or rules out a hypothesis	Used to create hypotheses; provides a resource that cannot fully be interpreted at time of testing, but that can be referenced over time	