J Assist Reprod Genet (2017) 34:967–973
DOI 10.1007/s10815-017-0938-y

FELLOW'S FORUM

Precision reproductive medicine: multigene panel testing for infertility risk assessment

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Received: 6 March 2017 / Accepted: 27 April 2017 / Published online: 3 May 2017

Abstract The concept of precision medicine relies on a thorough understanding of the consequences of unique features of individual patients, such as environmental exposures and genetic profiles. A key component of implementing individualized care in this paradigm will be improved assessment of genetic risk. Compared with single gene tests, multigene panel testing—which has recently become commercially available for female infertility—offers the possibility of a more comprehensive and efficient risk evaluation. However, as the use of multigene panel testing for breast cancer risk has shown, this approach must be used judiciously to ensure its usefulness in a clinical setting. Key challenges which have been encountered in oncology include the interpretation of gene variants of questionable clinical effect and a lack of evidence to guide management after variants are identified. In this review, the core concepts of multigene panel testing for risk assessment are discussed, with careful attention to both its shortcomings as well as its potential for benefit in reproductive medicine.

Keywords Precision medicine · Reproductive genetics · Multigene panel testing · Genetic predisposition to disease · Infertility

Introduction

The precision medicine movement seeks to integrate environmental, lifestyle, and genetic information to improve and personalize healthcare. This concept has been employed in many areas of medicine, ranging from oncology to psychiatry. Chemotherapeutic agents can be selected with consideration to a patient's genotype in order to maximize efficacy [1] and safety [2]. Genetic profiles have been identified which predict the necessary therapeutic dose for opioid analgesia [3] and the amount of heart disease risk reduction a patient will gain from statins [4]. Inspired by these early successes, the National Institutes of Health (NIH) has begun its Precision Medicine Initiative, a large-scale analysis of the biological underpinnings of health outcomes for one million study subjects [5].

One key objective of precision medicine is an improved understanding of who is at risk for particular diseases. Such information can serve several important purposes. First, more accurate risk assessment can refine screening guidelines, which are currently based primarily on a patient's age with modification for positive family history and behavioral or demographic risk factors. Improved assessment of genetic risk—even in the absence of relevant family history—can identify subgroups of the population whose risk for breast cancer or colon cancer would merit initiation of screening at a significantly earlier age than national standards currently recommend [6]. This knowledge can also motivate early interventions to prevent an undesired outcome, such as the use of risk-reducing surgery for patients with cancer risk alleles [7]. Finally, improved risk assessment can empower patients with knowledge about their future health risks, thereby motivating behavioral changes and careful consideration of overall life plans [8].

Since the completion of the Human Genome and HapMap Projects, there has been a significant increase in the number of identified genetic risk factors for a multitude of diseases. This knowledge has largely been driven by genome-wide association studies (GWAS) and deep sequencing of candidate genes using next-generation sequencing (NGS), which together

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provide a greater breadth of genomic coverage and a population-level approach to variant detection. The growing literature has allowed clinical genetic risk assessment to move beyond identification of merely the highest risk alleles, such as high-risk *BRCA1* and *BRCA2* variants (which confer a relative risk of greater than 11 for the development of breast cancer), to now also include moderate risk alleles in genes with less "name recognition," which increase disease risk by two- to four-folds [9]. A central concept in the clinical utilization of these moderate risk alleles is their frequent assembly into multigene panels, where a broad screen for 100 or more risk alleles can be performed simultaneously. Such multigene panel testing has become a common approach for cancer risk assessment [10] and has recently been introduced to assess the risk of problems with female fertility [11]. This review article seeks to evaluate the current state of multigene panel testing for risk assessment, highlighting its successes and shortcomings from other medical disciplines, in order to provide guidance for a responsible and appropriate adoption of this tool in fertility healthcare.

Genetic risk assessment with multigene panel testing: an overview

While genetic risk assessment has classically focused on high penetrance genes, such as *APC*, *TP53*, or *BRCA1* and *BRCA2*, patients without pathogenic mutations in such genes may have risk-bearing alleles at other genetic loci. For instance, in a small study of women referred for *BRCA1*/*BRCA2* testing (either due to a breast/ovarian cancer diagnosis or a strong family history), 11% of the women who tested negative for *BRCA* mutations were found to have likely pathogenic variants in other genes [12]. This work and similar findings [13, 14] have prompted the development and commercial availability of multigene test panels for risk assessment.

The paradigm of multigene panel testing is based upon three core premises. First, such tests aim to reduce the likelihood of a false negative assessment of genetic risk. If testing is limited to one high penetrance gene, there remains the significant possibility that a patient may have risk alleles which, although of lesser magnitude, serve to increase the patient's lifetime risk of disease beyond a general population risk [12]. Second, panel testing is generally a more cost-effective way to identify risk alleles for a particular disease, with cost savings from screening each risk allele individually and sometimes even a minimal cost increase from performing a single-gene test. Third, panel testing is a more time-efficient method to obtain genetic risk information. Rather than serially testing patients for risk alleles in a hierarchy of likelihood or penetrance, multiple risk alleles are able to be assessed in parallel, reducing the time from initial evaluation to completion of risk assessment [15].

It is important to note that multigene panel testing had been effectively employed in genetic diagnosis before its introduction into risk assessment. Diagnostic multigene test panels are available for a variety of clinical conditions, ranging from hypertrophic cardiomyopathy [16] to sensorineural hearing loss [17] and, in the realm of infertility, primary ciliary dyskinesia [18]. In each of these clinical conditions, mutations in multiple genes have been implicated in the pathogenesis of a single or overlapping clinical phenotype. While the same three core premises (i.e., decreasing the false negative rate, decreasing the cost, and increasing the time efficiency) underlie this form of multigene panel testing as well, the intention of such testing is to identify a pathogenic mutation in an affected individual, rather than the identification of a lower penetrance genetic risk factor in someone who may or may not be clinically affected.

Methodologically, multigene panel testing can involve a variety of techniques for the detection of pathogenic variants. NGS is a cost-efficient method for sequencing multiple genes at once and thus provides the basis for most multigene panel tests. While this sequencing is often performed over the entire coding region with partial coverage of the intervening intronic sequence [19], it can also be targeted (or masked) to simply detect known genetic variants of interest. Traditional Sanger sequencing may also be utilized in multigene panel testing, particularly for genomic regions with insufficient or poor-quality NGS coverage and for confirmation of novel variants detected with NGS [19, 20]. In addition, targeted chromosomal microarrays may be included for the detection of pathogenic deletions and duplications [19].

While the power of multigene panel testing lies in the amount of genetic information it provides, this level of detail carries some inherent downsides. When sequencing is not limited to the identification of known risk-conferring variants, there is a possibility of identification of variants of unknown significance (VUS), for which there is inadequate evidence (e.g., from family or population studies, prior instances of the variant, in vitro or in vivo functional studies, or in silico predictions of function) to remark on its pathogenicity [21]. A VUS is more likely to be detected when multiple genes are sequenced, making this a greater problem for multigene panel tests [22]. Both physicians and genetic counselors can struggle to explain the consequence of a VUS [23, 24], and patients feel less reassurance and higher disease-related anxiety when they are told they have a VUS [25].

In addition to the problem of VUS detection, multigene test panels also may include genes of unclear consequence. Although a gene will not be included in a test panel unless the literature suggests a significant association with disease risk, some of the studies which have inspired genes' inclusion in test panels have focused on specific subpopulations (e.g., specific ancestries or severe phenotypes) or lacked appropriate controls for accurate risk calculation [9]. Even when the

disease risk associated with a genetic variant is accurate, there often is a lack of evidence for a benefit or cost-effectiveness of subsequent interventions. Both patients and physicians may have heightened concern about the disease process for which they sought risk assessment, which may promote active interventions even when they are not of proven merit. Additionally, confusion about how relative risk relates to absolute risk of disease may give an incorrect impression about the magnitude of risk and inspire excessive intervention [6].

To balance the merits and drawbacks of multigene panel testing, several commentators have argued for a stricter application of the CDC's "ACCE" framework for genetic testing [9, 26]. This model considers the analytic validity, clinical validity, clinical utility, and ethical/legal/social issues surrounding a genetic test (Table 1). Analytic validity is the accuracy of variant detection by a given test, which all validated clinical genetic tests should provide. Clinical validity refers to the accurate knowledge of disease risk that a genetic test provides; this hinges upon well-conducted primary literature with applicability to the clinical test population. Clinical utility refers to the usefulness of genetic information for guiding action, such as making behavioral changes or choosing a risk-reducing intervention. Throughout the majority of the USA, neither clinical validity nor clinical utility needs to be demonstrated before a genetic test is introduced to the market [9], so clinicians and insurers must demand that these ACCE standards are met before a test is employed for a given patient. Finally, associated ethical, legal, and social issues should be considered for all genetic tests (even those that seem innocuous), due to the permanency of genetic identity and the limited understanding that we still have about the risks associated with genetic variation.

Table 1 Implications of the ACCE model on multigene test panels for infertility risk [9, 26]

ACCE element	Meaning	Implication
Analytic validity	Test accuracy at detecting a variant	Stringent QA needed in CLIA-certified lab
Clinical validity	Accurate measurement of disease risk associated with genetic variant	Gene panel interpretations must be limited to validated risk alleles applicable to the tested patient's ancestry
Clinical utility	Effect of the test result on next steps in patient management	Gene panel test results should be acted upon if they significantly impact the absolute risk of disease, or if known directed therapies are available
Ethical, legal, and social issues	n/a	Need to protect sensitivity of genetic information to avoid unethical uses of the information with damaging social implications (e.g., denial of fertility treatments, loss of social opportunities)

Genetic risk assessment for breast cancer with multigene panel testing

To understand the possibilities and perils of multigene panel testing, it is useful to look at the example of breast cancer risk assessment, the clinical arena where this approach has been most frequently utilized. Unsurprisingly, the greatest successes obtained from such testing come from the identification of the highest risk alleles and the subsequent interventions that follow. Now that gene patents have been invalidated and breast cancer risk panels can include *BRCA1* and *BRCA2*, mutations in these genes can be readily identified and acted upon. Risk-reducing salpingo-oophorectomy for women with *BRCA1* and *BRCA2* mutations is associated with decreased all-cause mortality (10 vs 3%), breast cancer-specific mortality (6 vs 2%), and ovarian cancer-specific mortality (3 vs 0.4%) [27].

Conceptually, it is sensible that expanded genetic testing may be of benefit for breast cancer risk assessment. Among women with a positive family history of breast cancer, only one-fifth to one-quarter will have mutations in *BRCA1* or *BRCA2* [28], so it is likely that variants in other genes also play an important role. Indeed, initial studies of multigene test panels suggest that women at high risk of breast cancer who lack mutations in *BRCA1* and *BRCA2* are 4.5 to 11% likely to have suspected pathogenic variants in other genes [10]. Many of these variants, in genes such as *CDH1*, *NF1*, *PALB2*, and *CHEK2*, are generally accepted as valid risk-conferring alleles [9]. However, even for many of the widely accepted risk alleles, there is no evidence or guideline to suggest a specific course of action, such as a change to breast cancer screening frequency or the pursuit of risk-reducing surgery. Thus, family history alone often provides as much guidance for clinical counseling as the more detailed genetic information provided by multigene test panels [10].

In addition to the limited actionability of many validated risk variants for breast cancer, many multigene test panels include genes and variants of unclear risk. These genes frequently have biological plausibility, such as DNA mismatch repair genes, but their association with disease risk is less conclusive. This may be due to conflicting publications in the literature, with supportive literature refuted by later findings of no association; inappropriate statistical analysis, such as a lack of multiple test correction; and publication bias favoring studies suggestive of significant associations [9]. It is likely that most clinicians will not be able to remark on the quality of data that underlies a stated risk for an allele on a

multigene test panel, due to the specialized knowledge and time that this would require. Additionally, risk alleles on multigene test panels may be originally identified in more extreme phenotypes and in families with several affected family members; neither of these scenarios may be applicable to the unaffected patient desiring to understand her risk of disease. Due to these concerns, many breast cancer experts have recommended caution with the use of large multigene test panels for risk assessment and judicious, data-driven use of their results, preferably after well-informed pre- and post-test counseling [9, 10].

Genetic risk assessment for causes of infertility with multigene panel testing

Focused gene panels (such as those offered by Centogene and EvolveGene) can identify pathogenic genetic variants for patients with specific infertility phenotypes, such as ovarian dysgenesis or azoospermia, and screen for rare mutations which directly cause overt infertility, such as impaired oocyte maturation and fertilization defects. However, genetic assessment for infertility risk (rather than diagnosis of Mendelian fertility disorders) has been predominantly focused on screening for the *FMR1* premutation to identify a risk of primary ovarian insufficiency [29]. More recently, multigene panel testing for risk assessment has been introduced into the field of reproductive medicine [11]. The first commercially available product in the USA, Fertilome (Celmatix Inc., New York, NY), uses masked analysis of targeted next-generation sequencing to examine 49 specific single nucleotide variants in 32 genes which have been implicated in a variety of reproductive conditions, such as primary ovarian insufficiency (POI), recurrent pregnancy loss (RPL), polycystic ovary syndrome (PCOS), and endometriosis [30]. In accordance with the recommendations of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology, the sequencing is performed in a Clinical Laboratory Improvement Amendments (CLIA)–approved laboratory [21]. By limiting the genetic analysis to only selected variants, the Fertilome panel avoids the dilemma of VUS detection that encumbers many multigene test panels.

Conceptually, multigene panel testing for infertility risk assessment is similar to its use in breast cancer. Powered by decreasing costs for genetic sequencing, it provides a more comprehensive evaluation of risk alleles in a time-efficient fashion. Similar to breast cancer multigene test panels, infertility risk test panels go beyond the highest risk variants to include variants with a more moderate risk of a fertility problem. For instance, while the more commonly tested *FMR1* premutation confers an odds ratio of POI of greater than 20 [31], the currently available infertility multigene panel includes variants with odds ratios ranging from 1.5 to 4.5 for the development of POI.

When evaluating multigene panel testing for infertility risk assessment, the same ACCE model (Table 1) discussed for breast cancer risk assessment should be upheld, and the same caveats should be considered. Importantly, hesitation should be taken before recommending an action based upon alleles of unclear consequence. For example, Fertilome assesses for rs254286, a synonymous coding variant located within the *GDF9* gene; this variant has a stated odds ratio of 1.54 of developing POI. However, the risk reported by Fertilome is based upon a meta-analysis of only two publications; these studies were performed on women of exclusively South and East Asian ancestries, thus calling its generalizability into question [32, 33]. Furthermore, one of the studies cited by Fertilome to establish this polymorphism as a POI risk allele used inappropriate controls (i.e., included women as young as 22 years old, thus lacking assurance that they will not eventually develop POI) [33] while the other did not adequately describe their controls [32]. Poorly selected controls diminish the accuracy of the resulting odds ratio. These issues underscore the importance of knowing a test's clinical validity when counseling a patient about the results of any multigene test panel.

In addition to clinical validity, a second core component of the ACCE framework which should be considered is the clinical utility of multigene panel testing for infertility risk assessment. Ideally, interventions offered on the basis of the multigene panel test results would be driven by evidence; however, the majority of the alleles included in current infertility test panels lack data on outcomes from interventions driven by their identification. For instance, it remain unclear what specific interventions could currently be suggested on the basis of discovering a polymorphism in the *AR* (androgen receptor) gene in a patient with a history of RPL, as there is no trial in humans to show benefits for any targeted therapies. While there may be a benefit to identifying a risk allele for managing patient expectations [34], it is not even clear whether the use of a gestational carrier would benefit a patient with an *AR* risk allele, as there is neither human outcomes data on such an approach nor a full understanding of the mechanism of action of *AR* variants in RPL [35].

In the absence of data on the value of interventions prompted by an identified risk allele, clinical utility can also be hindered by a misunderstanding of the absolute risk associated with a given variant. For instance, if an allele has an odds ratio for POI of 1.5, the absolute risk of POI for a person with that allele is only around 1.5%. While additional studies could be done to characterize the cost-effectiveness of fertility preservation for patients with this allele, the low absolute risk it confers suggests that it is unlikely to be of clinical utility. Thus, when lacking evidence of a benefit for allele-driven interventions, it becomes imperative for the ordering provider

to carefully consider the likely clinical significance of a risk allele when counseling a patient about the next steps in care.

Because genetic risk can be challenging for patients to understand, it is essential that thorough and informative pre- and post-test counseling be provided with any genetic risk assessment. This counseling can ensure that patients have an opportunity to clarify the potential (and actual) findings of the genetic test and to understand their implications. Beyond aiding their understanding of the test's clinical validity and utility, such counseling can also help patients to better understand the possible ethical, legal, and social implications of the test [36]. For instance, patients may not realize that identification of a risk allele in their own genome may give them an ethical argument to share their private health information with relatives who may unknowingly have the same genetic risk. Additionally, patients may not recognize the limitations of the Genetic Information Nondiscrimination Act of 2008 (GINA), which prohibits discrimination in employment and health insurance, but offers no legal protection from increased disability insurance premiums or decreased access to life insurance [37]. Thus, when ordering Fertilome or any other multigene risk panel, it is imperative for the ordering physician to provide genetic counseling or refer the patient to a trained genetic counselor. Such counseling is necessary to ensure that the patient is well-informed about all possible implications and benefits before pursuing genetic testing.

Precision reproductive medicine: looking towards the future

Although some authors are skeptical that precision medicine will truly be able to improve the prediction and prevention of common diseases through identification of genetic risk alleles [38], the decreasing cost of DNA sequencing and the financial investment of the US Precision Medicine Initiative suggest that disease prediction of this sort will be thoroughly attempted. As a means to this end, it is likely that multigene panel testing will grow in its popularity throughout reproductive medicine and beyond. In the near future, we can expect to see studies characterizing the usefulness of multigene test panels for risk assessment. Important qualities to understand include the proportion of tested women who have clinically actionable alleles and the cost-effectiveness of pursuing multigene panel testing in relation to subsequent interventions; both of these features have illuminated the appropriate use of genetic risk assessment for breast cancer [39, 40].

While multigene panel testing offers the powerful potential of identifying multiple risk alleles for a limited increase in cost over single-gene sequencing, the caveats acknowledged by oncologists about this technology [9, 10] need to be heeded in reproductive medicine as well. Most importantly, the ACCE model must be used to evaluate and improve multigene panel risk assessment (Table 1). This demands a close scrutiny of the literature from which risk alleles have been identified to ensure clinical validity. The robustness of multigene panel test results would further benefit from independent validation studies for each risk allele [38]. In reproductive medicine, we only have to look as far as FISH-based preimplantation genetic screening ("PGS 1.0") [41] and metabolomics profiling with NIR spectroscopy [42] to see the necessity of validation before widespread utilization of a new assay. Such validation would preferably be carried out in an ethnically admixed population to ensure generalizability of the results. Additionally, multigene panel risk assessment would be made more useful by further studies that evaluate the benefits of interventions targeted to specific genotypes. These studies would likely require large sample sizes in order to demonstrate moderate benefits for women with moderate risk alleles; for comparison, 170 patients with the high-risk *BRCA1* and *BRCA2* alleles were needed to demonstrate the large benefits of risk-reducing salpingo-oophorectomy [43]. However, such evidence of clear clinical utility for the information derived from multigene test panels would provide the necessary grounding for the ordering provider to recommend a subsequent action.

Ultimately, the true potential of multigene panel testing for infertility risk assessment is likely to be obtained after several important advances in the field of genomics. One key advancement would be the development of polygenic risk scores for various fertility-impairing conditions. Polygenic risk scores integrate the individual impact of all the genetic variants that a patient carries into one measure of disease risk [6]. Because multigene panel tests allow the opportunity for identification of many risk alleles simultaneously, it will be important to know the resulting risk if several variants are uncovered in the same patient. The polygenic risk score may increase the utility of identifying even low- to moderate-risk alleles, provided that they contribute to a net risk of disease that is more clinically relevant. Beyond large-scale studies to characterize the effect of combining multiple risk alleles, polygenic risk scores will also benefit from increased research on protective alleles, an area of genetics which has historically been underemphasized [44]. Such protective alleles may counter the risk conferred by deleterious variants and decrease the overall polygenic risk score [45].

Another key genomic advancement which will make multigene test panels more clinically useful is refinement of genotype-phenotype correlations. Many public databases exist which report phenotypes attributed to genetic variants. However, a study of incidental findings from exome sequencing revealed that less than 10% of the variants considered "disease-causing" in a large public database were actually likely to be pathogenic [46]. Additionally, while variants found via NIH-funded research must be reported to public

databases such as ClinGen and ClinVar, commercial laboratories are not obligated to report to the same databases. Furthermore, these public databases do not generally contain detailed phenotypic information about the person who has the variant, but rather a more limited description of their phenotype [47]. Increased availability of detailed phenotype information for genetic variants will be invaluable for improving the clinical validity of multigene test panels.

Finally, the clinical utility of multigene panel testing will likely grow with increased research on the pharmacogenomics of infertility. To date, preliminary trials have investigated alleles associated with increased rates of spontaneous ovulation for PCOS patients on metformin [48] and genotypes which may benefit from low molecular weight heparin for the prevention of pregnancy loss [49]. Additionally, distinct variants in the *FSHR* gene, which encodes the FSH receptor, have been associated with a propensity for OHSS or poor response to controlled ovarian hyperstimulation [50]. Further research on fertility pharmacogenomics would allow the discovery of genetic risk to manifest in personalized treatments, accomplishing the idealized precision medicine paradigm.

Conclusions

The increased availability of low-cost DNA sequencing is one of several factors which has brought us to the advent of an era of precision medicine. Capitalizing on this low-cost sequencing, multigene panel testing is a streamlined method for genetic risk assessment which has recently entered the realm of reproductive medicine. As we consider how to appropriately make use of such a tool in fertility healthcare, it is valuable to learn from the challenges described by oncologists when employing similar approaches to breast cancer risk assessment. There, the benefits of a more comprehensive evaluation of pathogenic variation have been countered by the difficulties brought by risk assessments based upon questionable primary literature and a lack of actionability for many of the results. Further studies into the clinical utility and cost-effectiveness of multigene panel testing for infertility risk, as well as basic research to validate the included alleles and identify their mechanism of action, will make such risk assessment more attractive for clinical use. With continued research on polygenic risk scores, genotype-phenotype correlations, and pharmacogenomics applications, it is likely that multigene test panels will eventually serve an important role in bringing precision medicine to the treatment of infertility.

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

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