The Economic Burden of Genetic Tests for the Infertile Male: A Pilot Algorithm to Improve Test Predictive Value

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Abbreviations and Acronyms

C-index = concordance index

FSH = follicle-stimulating hormone

LH = luteinizing hormone

NOA = nonobstructive azoospermia

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Purpose: We developed a model to optimize genetic testing in infertile men with nonobstructive azoospermia and severe oligospermia. We also assessed the optimal cutoff value of the predicted probability of advising genetic testing and evaluated the direct cost saving of using the model.

Materials and Methods: We retrospectively reviewed the records of infertile men who underwent Y microdeletion and karyotype testing at our fertility center from 2006 to 2012. Semen parameters, testicular volume, testosterone, luteinizing hormone, follicular stimulating hormone and varicocele were assessed as potential predictors of genetic disorders. We fitted logistic regression to all predictors and selected a nomogram based on the concordance index and calibration. We calculated the cost saving of using the model.

Results: Of 325 patients 278 fulfilled study inclusion criteria, including 27 with an abnormal karyotype, 11 with a Y microdeletion and 1 with each condition. We developed a nomogram using sperm concentration and motility, testicular volume and serum testosterone level. The nomogram concordance index was 0.738. The optimal cutoff value was 13.8% with 0.788 sensitivity, 0.590 specificity, 0.245 positive predictive value and 0.943 negative predictive value. Testing men above the 13.8% cutoff resulted in a direct 45% cost saving. However, 15.4% of genetic anomalies were missed, including 2 Y microdeletions.

Conclusions: Using common clinical and laboratory parameters our nomogram detects 84.6% of genetic anomalies. Nomogram use resulted in a 45% direct cost saving but carries the risk of missing pertinent genetic abnormalities.

Key Words: testis, nomograms, azoospermia, male sterility due to Y-chromosome deletions, chromosome aberrations

Genetic testing is valuable to determine the etiology of infertility and predict the success of sperm retrieval procedure in patients with NOA and severe oligospermia. In addition, early diagnosis of genetic syndromes such as Klinefelter syndrome may mitigate long-term detrimental health effects. The prevalence of genetic disorders in infertile males varies by study population. However, chromosomal abnormalities are found in 10% to 15% of men with azoospermia and 5% with severe oligospermia.[1,2] Y microdeletions are found in 7% to 10% of men with azoospermia and severe oligospermia.[2]

Sperm concentration correlates with the chance of a positive genetic test but the optimal concentration for predicting a positive genetic test has yet to be determined. Practice patterns for obtaining genetic testing vary among institutions. Current American

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Urological Association guidelines recommend karyotype and Y microdeletion testing in men with primary infertility, no prior sperm concentration greater than 5 million per ml and no suspicion of obstruction.[2] However, Stahl et al found that the rate of Y microdeletions in men with a sperm concentration of between 0 and 1 million per ml was 10% while the rate decreased to only 1.7% in those with a concentration of between 1 and 5 million per ml.[3] Similarly, in a study of 1,997 men with NOA or severe oligospermia, defined as a sperm concentration of 5 million per ml or less, only 2 of 99 Y microdeletions were found in men with a concentration of greater than 2 million per ml.[4] In this study to be cost-effective we defined severe oligospermia as 2.5 million sperm per ml or less. Our current practice is to perform genetic testing in men with a sperm concentration of less than 2.5 million per ml.

As the cost of health care continues to increase, clinicians and institutions face mounting pressure to contain cost while not compromising care. At our institution Y microdeletion and karyotype testing costs $517 and $2,070, respectively, for a total cost of $2,587. Based on a 10% to 15% prevalence between $18,109 and $25,870 is spent to find 1 male with a positive genetic test. This expense represents a significant economic burden. Therefore, a model that better predicts the chance of a positive genetic test would be beneficial to clinicians and infertile couples alike.

Our primary objective was to develop a predictive model using common clinical and laboratory parameters to better predict the probability of a positive genetic test. As part of this objective, we investigated the optimal cutoff point on the nomogram predictive scale to perform genetic testing in this population.

Our secondary objective was to investigate the potential cost saving using the model vs using the current standard. To our knowledge this is the first study of a nomogram to predict a positive genetic test in men with NOA and severe oligospermia, and of the cost saving of using this model.

MATERIALS AND METHODS

The study was approved by our institutional review board. The electronic medical record was queried for men 18 years old or older who sought fertility evaluation from December 2006 through April 2012 and completed karyotype and/or Y chromosome microdeletion testing. Those with a sperm concentration of 2.5 million per ml or less on all semen analyses performed at our facility were included in study. In addition to semen results, we retrieved the date of birth, total serum testosterone and serum gonadotropin levels (LH and FSH). When men underwent multiple iterations of the same test, the test dated closest to the initial clinic visit was used in our analysis.

Charts were reviewed manually to retrieve testicular volume and the presence of clinical varicocele. Total testicular volume was calculated by adding right and left testicular volumes, as assessed by an orchidometer based physical examination. If a testicle were missing, the volume of the solitary testicle was doubled. We presumed that the missing testicle would have been similar in size if it were present, because most etiologies of NOA and severe oligospermia, eg Klinefelter syndrome, Y microdeletion and balanced translocations, do not result in asymmetrical testes.

Sperm concentration was used to categorize cases as azoospermic or severely oligospermia. Men who required pelleting to detect sperm were categorized as having azoospermia and assigned a concentration of zero for analysis. However, when motility was available, it was included in analysis. Genetic testing outcome was defined as positive if karyotype or Y microdeletion was positive.

Between group comparisons for continuous variables was done with the Wilcoxon rank sum test except as noted. Categorical variables were compared with the chi-square or Fisher exact test. One man with a karyotype and a Y microdeletion defect was excluded from subanalysis comparing Y microdeletion cases to karyotype positive cases. Logistic regression was fitted to all relevant predictors. Restricted cubic splines were used for continuous predictors to account for the nonlinear effect. Model selection was based on the prediction performance or C-index. The model with the highest C-index was chosen as the final model. The nomogram was then constructed for the final model. The C-index was calculated by internal bootstrap sampling. Calibration of the final model was also checked. We used R, version 3.0.0 (http://www.r-project.org/). The optimal cutoff on the nomogram predictive scale was based on sensitivity, specificity, and positive and negative predictive values.

The total cost in the cohort of men who underwent genetic testing was compared to the cost if only men above the optimal cutoff point were tested. Cost saving was calculated as the difference in these 2 values. The cost of each test at our institution is $517 for Y microdeletion and $2,070 for karyotype analysis for a total of $2,587 per patient. The Y microdeletion panel tests for deletions in the AZFa, AZFb and AZFc regions.

RESULTS

The electronic search retrieved 325 candidates, of whom 278 fulfilled inclusion criteria and comprised our study group. Figure 1 shows the genetic findings and distribution by concentration category. NOA was present in 169 men (60.8%), 107 (32.9%) had severe oligospermia and in 2 the sperm concentration was not in the electronic medical record. A genetic abnormality was found in 39 study patients (14%), including 27 (9.7% overall) with abnormal karyotype, 11 (4.0%) with Y microdeletions and 1 (0.4%) with each condition. Klinefelter syndrome was the most common defect (15 cases), followed by AZFc deletions (8). All men with Y microdeletions were categorized as having azoospermia.