OBJECTIVE: To investigate contemporary national trends in the diagnosis and management of varicoceles, and identify the most important predictors of varicocele repair.

DESIGN: Population-based retrospective cohort.

MATERIALS AND METHODS: The MarketScan Commercial Claims and Encounters database was queried using relevant CPT, ICD9, and HCPCS codes to identify all 18-45 year old men diagnosed with a varicocele during 2009-2015. Differences in age, clinical characteristics, geographic distribution, and medical management between men who did and did not undergo varicocele repair during the study period were compared using unpaired t-tests and Chi-squared tests for continuous and categorical variables, respectively. Multivariable logistic regression analysis was used to evaluate age, geographic location, and use of semen analysis, hormone analyses, and ultrasound, as predictors of varicocele repair. SAS v.9.4 was used for all statistical analyses. Significance was set at $p<0.05$.

RESULTS: Of the 21,195 men were diagnosed with a varicocele between 2009-2015, 8231 (39%) underwent surgical repair, using either an open (82%), microsurgical (11%), or laparoscopic approach (7%). Men who underwent varicocele repair were more likely to have a diagnosis of male infertility compared to those who did not undergo repair (15 vs. 8%), and were more likely to have complete semen analyses (36 vs. 12%) and serum testosterone evaluation (43 vs. 19%). Use of gonadotropin therapy, selective estrogen receptor modulators, and aromatase inhibitors was also more common among men who underwent varicocele repair. In multivariable regression models, the strongest predictors of varicocele repair were semen analysis evaluation (OR 3.13, 95% CI 2.9-3.38), age 18-25 (OR 2.65, 95% CI (2.37-2.96), and serum testosterone evaluation (OR 2.64, 95% CI 2.46-2.84).

CONCLUSIONS: Male hypogonadism is emerging as an important and independent predictor of varicocelectomy among U.S. men. The most common approach to varicocele repair remains open ligation, followed by microsurgery, and then laparoscopy.

O-110 Tuesday, October 31, 2017 11:15 AM

PATERNAL AGING OVER A NATURAL LIFETIME IS DIRECTLY ASSOCIATED WITH GENETIC AND EPIGENETIC ALTERATIONS IN THE MALE GAMETE. M. Katz-Jaffe, J. C. Parks, B. R. McCallie, M. Denomme Tignanelli, W. B. Schoolcraft. Colorado Center for Reproductive Medicine, Lone Tree, CO.

OBJECTIVE: There is evidence that a combination of genetic mutations and epigenetic alterations may support an association between paternal age at human conception and neurodevelopmental disorders in offspring, including autism and schizophrenia. The aim of this study was to investigate the exome and methylome of individual male gametes over the course of a natural lifetime.

DESIGN: Longitudinal animal study.

MATERIALS AND METHODS: This study examined sperm of individual male mice over their natural lifetimes from youth (5 months) to old age (15 months). Young males (5 months) with proven virility had 1 testicle surgically removed for mature sperm collection. Fecundity was then assessed monthly, utilizing young virgin females (6-8 weeks) to control for any female factor. The remaining testicle was excised for mature sperm collection when the male reached old age. Individual sperm samples were subjected to somatic cell lysis prior to sperm DNA isolation for exome sequencing (ION PI v2 chip; Thermo Scientific) and methylome analysis (Mouse Genome Microarray 2x105K; Agilent Technologies). DNA sequence reads were aligned to mouse reference genome UCSC mm10 and compared to UCSC dbSNP 137 with Avadis NGS platform. Methylome statistics utilized a BATMAN algorithm (Bayesian Tool) to calculate methylated or unmethylated probes, significance at $P<0.05$.

RESULTS: All males experienced significantly reduced fecundity with old age (15 months) and no viable offspring were produced after 12 months. Sperm exome sequencing generated 75 million reads, high coverage and 99.5% accuracy in single base nucleotide calls. A total of 625 de novo point mutations resulting in direct amino acid changes were detected only in older age sperm (12-15 months) and never observed in sperm from these same males during their youth ($P<0.05$). The amino acid changes are predicted to impact protein/enzyme function, and pathway analysis of the 625 de novo point mutations revealed enrichment of genes involved in neurological system pathways. Significant methylation alterations were also observed with paternal aging across the genome and on every chromosome. Specifically, 308 probes lost methylation (85 promoter regions) and 102 probes gained methylation (35 promoter regions), in older age sperm when compared to the sperm collected in their youth ($P<0.05$). Methylation validation using targeted bisulfite mutagenesis confirmed alterations with paternal aging in Pex7, a gene associated with autism ($P<0.05$).

CONCLUSIONS: This novel study examined sperm DNA over the natural lifetime of an individual male revealing an accumulation of de novo point mutations in the spermatozoa coding sequence, as well as significant methylation alterations. Combined, these sperm DNA changes associated with paternal aging are predicted to have severe consequences to downstream gene transcription and cellular signaling in the offspring, thereby impacting developmental pathways including early stages of neurodevelopment.

O-111 Tuesday, October 31, 2017 11:30 AM

INVESTIGATING THE ROLE OF SPERM-SPECIFIC RNA TO SCREEN MEN WITH UNEXPLAINED INFERTILITY. N. Pereira, S. Cheung, A. Parrella, C. O'Neill, N. Nikprelevic, Z. Rosenwaks, G. D. Palermo. The Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine, Weill Cornell Medicine, New York, NY.

OBJECTIVE: To identify the compartmentalization of candidate gene clusters within the human spermatozoon that contribute to spermatozoal fertilization capacity and embryo developmental competence.

DESIGN: Sequencing and differential expression of sperm-specific RNAs in men with unexplained infertility.

MATERIALS AND METHODS: Consenting men screened for infertility donated their ejaculated semen samples during a 15-month period. Donors with proven fertility served as controls. RNA was isolated from $25x10^6$ human spermatozoa using a commercially available spin column kit. Spermatozoal RNA concentration was subsequently assessed. Illumina stranded RNA sequencing (RNA-Seq) library preparation was used to construct paired-end libraries. Pilot sequencing was expanded to 50-60M reads at 2x76bp. RNA expression was calculated in fragments per kilobase of transcript per million mapped reads (FPKM). Differentially expressed RNA transcripts were identified and classified into gene clusters based on sperm-specific components i.e., the acrosome, nucleus, mid-piece, and flagellum. The expression of these transcripts was compared with standard semen parameters, and between the study and control groups.

RESULTS: Thirty-one men with a mean age of 39.6 ± 5 years had the following semen parameters: 46.3 ± 19 x 10^6/mL concentration and 44.8 ± 14% motility. The age of the female partner in the study and control groups was comparable. Differentially expressed RNA transcripts between the study and control groups were grouped into sperm-specific clusters: *DPY19L2* and *ATP6V1E2* (acrosomal); *APLF*, *CYUB5R4*, *ERCC4*, *MORC1*, *PIWIL1*, *TNFRSF21*, *TSSK6* and *H1FNT* (nucleus); *ADCY10*, *SMCP*, *PLK4* and *AGPAT2* (mid-piece); and, *AKAP4* and *CATSPER1* (flagellum). There was a strong correlation between the expression of *ATP6V1E2* and fertilization rates (R^2 0.63; $P<0.001$) in men who underwent ICSI. A positive correlation between *AKAP4* and motility was also noted (R^2 0.40; $P=0.01$). The gene cluster localized to the nucleus was significantly under-expressed in the study group when compared to the control group ($P<0.001$). Interestingly, the expression of *APLF*, *CYUB5R4*, *ERCC4,* and *TNFRSF21* was found to be higher in men $\leq$40 years (47.2 ± 15 FPKM) compared to those >40 years (13 ± 9 FPKM; $P=0.02$).

CONCLUSIONS: Functional assessment of the gene cluster specific to certain compartments of the human spermatozoon may supplement standard semen analysis and serve as a vital tool in the diagnosis of unexplained infertility. This may further facilitate tailoring of assisted fertility treatments, thereby reducing the time to pregnancy.

O-112 Tuesday, October 31, 2017 11:45 AM

METABOLIC AGE VERSUS CHRONOLOGIC AGE EFFECT ON THE GONADAL STATE. A. Majzoub,[a] R. A. Talib,[a] O. Canguven,[a] H. Elbardisi,[a] M. M. Arafa,[a] K. Khalafalla,[b] S. S. Alsaid.[a] [a]Urology, Hamad Medical Corporation, Doha, Qatar; [b]Hamad Medical Corporation, Doha, Qatar.

OBJECTIVE: Hypogonadism or the decreased functional activity of gonads is a common medical condition among ageing men. Nonetheless, it is increasingly being detected among a considerable number of