Genetic evaluation for male infertility: Urology office practice

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Causes of Male Infertility

- Unexplained: 34%
- Varicocele: 17%
- Sexual Factors: 6%
- Urogenital Infection: 9%
- Undescended Testicles: 8%
- Systemic Disease: 3%
- Hypogonadism: 10%
- Immune System Factors: 5%
Men with azoospermia or severe oligozoospermia (<5 million sperm/mL ejaculate fluid) are predisposed to genetic abnormalities.

Genetic testing may reveal the aetiology and likelihood of successful paternity, and potential risks to offspring.

The cause of infertility can be demonstrated in approximately 20-30% of men with severe oligozoospermia or azoospermia.

Up to 80% remain with an unknown genetic cause requiring additional research to identify candidate gene.
* karyotype/cytogenetic testing
* Y chromosome microdeletion (YCMD) screening
* cystic fibrosis transmembrane conductance regulator (CFTR) gene screening
* congenital hypogonadotrophic hypogonadism (HH) mutation screening
- YCMD, located on the long arm of the Y chromosome (Yq),
- three azoospermic factor (AZF) regions associated with spermatogenesis.
- YCMD are not typically identified on standard karyotypic analysis due to small size, but instead are detected by PCR amplification (using DNA extracted from peripheral blood)
- YCMD is found in ONLY 5-10% men with severe oligospermia
  10-20% men with NOA

- Sixty percent of YCMDs do not result in retrievable sperm with TESE
- include all men with deletion of AZFa (Sertoli cell only syndrome)
  AZFb (maturation arrest) and
  AZFb+c (maturation arrest)
- none of which have had sperm identified to date with TESE in the few available studies
Among infertile men, AZFc is the most frequent have retrievable sperm 70% to 80% of the time and IVF/ICSI results are comparable to controls.

However, it is important to note that AZFc microdeletions are transmitted from affected fathers to all sons resulting in compromised fertility potential.
NO genetic testing

- 2ry infertility
- > 5 million sperm
- Normal semen volume
- Vasa felt

Obstructive
Normal testis volume + Normal FSH

- Low semen volume
  OR
- Vasa not felt

CFTR test wit partner testing
Non Obstructive

* Low testis volume + High FSH = 1ry testicular failure

Karyotyping
Y chromosome Microdeletion

(+/− CFTR if low semen volume)

Non Obstructive

* Low testis volume + Low FSH, LH, T = 2ry testicular failure

e.g. KAL 1
Is it just a click or tick box?

- 28% Not indicated
- 2ry infertility
- More than 5 Million sperm

- Among those indicated (N=144)
  3 Klinefelter
  2 Cystic fibrosis
  2 YCMD
Genetic testing is indicated only in men with azoospermia or severe oligozoospermia (<5 million sperm/mL).

Initial assessment should guide your decision whether or not to ask for genetic testing.

Proper counselling is essential.