

# Repromedix YCMD 3.0

## The Latest in Y Chromosome Deletion Testing



**Repromedix**<sup>®</sup>  
HELPING DOCTORS HELP COUPLES<sup>®</sup>

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Many clinicians demand Repromedix for their Y chromosome testing to avoid the high error rates of other laboratories and offer their patients the best information available.

“A Y chromosome microdeletion assay and karyotype should be performed on any male with severe oligospermia or non-obstructive azoospermia prior to operative intervention or use of the sperm for ICSI. These tests can avoid unneeded interventions and help couples make informed choices.”

ROBERT OATES, M.D.<sup>1</sup>  
Reproductive Urologist  
Boston University Medical Center

### Y chromosome deletion testing improves clinical management for up to 1 in 5 azoospermic and 1 in 10 severely oligospermic men

#### HOW TESTING IMPROVES CLINICAL MANAGEMENT

- Identifies candidates for TESE (testicular sperm extraction)
- Indicates need for genetic counseling regarding transmission of infertility
- Enables informed decisions about PGD
- Establishes cause of decreased sperm count, potentially reducing need for further investigation or treatment – for example: hormone treatment, varicocelectomy
- Provides answers to couples to help resolve feelings of guilt, blame, and stress

### Repromedix provides unparalleled information and support

#### ONLY REPROMEDIX YCMD 3.0

- Eliminates the high false positive rates of other laboratories
- Identifies over 48% more deletions of clinical importance
- Partners with the Page Laboratory at MIT to provide access to the latest testing systems

#### REPROMEDIX HAS THE LATEST AND MOST ACCURATE INFORMATION

- Repromedix is the only laboratory with the exclusive license to the Y chromosome deletion testing system from the Page Laboratory at MIT, the originators of Y chromosome deletion testing
- Y chromosome deletion testing is not a static field. Repromedix, in collaboration with MIT and clinical experts, continually updates and improves the Y chromosome deletion testing system and clinical interpretations

#### REPROMEDIX OFFERS FREE EXPERT CONSULTATION

- Repromedix consults with world leaders in science and clinical medicine to provide physicians with answers to questions and to help solve difficult clinical cases

#### REPROMEDIX PROVIDES UNIQUE AND COST EFFECTIVE SERVICES

- Easy sample requirements, either ambient whole blood or buccal swab.
- Phlebotomy services available for blood sample collection
- Direct insurance billing and the Safeguard program assure patient financial protection and satisfaction

# Y Chromosome Deletion Testing by Repromedix

## ELIMINATE FALSELY DIAGNOSED DELETIONS:

MANY DELETIONS REPORTED BY OTHER LABORATORIES ARE INCORRECT

Repromedix YCMD 3.0 avoids the high rates of incorrect Y chromosome deletion reporting by other laboratories. These errors can lead to incorrect clinical management of an infertile couple and affect their decision to use donor sperm or pre-implantation genetic diagnosis (PGD) <sup>1</sup>. Many physicians believe that the high error rates of other laboratories are unacceptable, and therefore will only use Repromedix YCMD 3.0.

**Quality of Primer Sequence:** Many other laboratories still use unreliable PCR primer pairs that identify non-existent deletions (such as the purported AZFd region identified by certain sequence tagged sites [STSs]) <sup>2,3</sup>. A review of the scientific literature reveals that unreliable primer pairs often fail to amplify and lead to reports of spurious deletions. For example, a study of 514 infertile men, using STSs that did not amplify reliably, identified 13 men (2.5%) with deletions only in the non-existent AZFd region <sup>2</sup>. Since about 12% of azoospermic/severely oligospermic men have Y deletions that would be detected by other panels, as many as 20% (2.5% / 12%) of positives reported by other laboratories may be incorrect <sup>2</sup>.

**Quality of Panel Design:** Even when primers associated with the AZFd region are eliminated, other laboratories have an up to 5% misdiagnosis/error rate <sup>4</sup>. Repromedix YCMD 3.0 contains a proprietary panel design which uses additional, confirmatory STSs and STSs positioned within critical spermatogenesis genes. Consequently, Repromedix YCMD 3.0 identifies Y chromosome deletions with fewer false positives and higher detection rates than any other system available.

## DETECT MISSED DELETIONS:

REPROMEDIX IDENTIFIES OVER 48% MORE Y CHROMOSOME DELETIONS OF CLINICAL IMPORTANCE

The Page Laboratory at MIT has identified new deletions of demonstrated clinical importance that occur frequently in azoospermic and oligospermic patients. This laboratory, along with several clinical and scientific collaborators, had generated the original Y chromosome

information upon which all commercial systems are based. Repromedix, in partnership with MIT and the Page Laboratory, has developed an updated and proprietary testing system: Repromedix YCMD 3.0. The testing system detects these additional Y chromosome deletions of recently established clinical importance (48% more in azoospermic patients [5.8%/12.1%]; 78% more in oligospermic patients [5.1%/6.5%]).

## IMPROVE CLINICAL MANAGEMENT:

HOW DO THE NEW DELETIONS IDENTIFIED BY REPROMEDIX YCMD 3.0 IMPROVE CLINICAL MANAGEMENT?

- 1. Repromedix YCMD 3.0 correctly diagnoses 9.1% (1.1% / 12.1%) more men with regard to use of testicular sperm extraction (TESE):** Repromedix YCMD 3.0 now identifies azoospermic or oligospermic men that have distal terminal deletions and several other newly identified miscellaneous deletions. Identifying these deletions informs men as to the cause of their infertility, the probability of success with TESE, and the benefit of using PGD to avoid passing on the deletion to their children <sup>1,5-7</sup>. Repromedix YCMD 3.0 identifies a number of other mutations for which Repromedix offers expert advice.
- 2. Repromedix YCMD 3.0 detects possible increased risk of testis cancer in azoo/oligo-spermic patients:** Only Repromedix identifies the gr/gr mutation (found in one of three oligospermic or azoospermic men with Y deletions), which identifies patients with a possibly 3 fold increased risk of testis cancer. Recently, a large well-designed study of 1807 men with testis cancer and 2599 cancer-free controls demonstrated that the gr/gr mutation was associated with a 3 fold increase in the occurrence of testicular germ cell tumors when a family history of testis cancer was present and a 2 fold increase without a family history <sup>8</sup>. When a study sample size is small, clinical application of genetic associations generally depends upon two independent studies. However, the above study is large, and furthermore, is not likely to be repeated in the near future. Therefore, physicians may want to use this information to identify high risk males who may then benefit from testicular examination.

According to the National Cancer Institute, "Most testicular cancers are first detected by the patient, either unintentionally or by self-examination. Some are discovered by routine physical examination." Testicular cancer occurs in 1 of every 280 men of European descent (with 77% diagnosed during the reproductive years of 20-44) <sup>9</sup>. Early diagnosis results in a 99.5% 5 year survival rate and a 60 fold reduction in mortality (~30% for metastatic versus 0.5% localized <sup>9</sup>). Because about one in 25 azoospermic or severely oligospermic men have the gr/gr mutation, testing with Repromedix YCMD 3.0 may help identify at risk males. Find further information at: <http://seer.cancer.gov/statfacts/html/testis.html> <sup>9</sup>.

- 3. Repromedix YCMD 3.0 detects more cases in which risk of low sperm count will be transmitted to sons:** The gr/gr deletion also indicates that a strong risk for azoospermia or severe oligospermia will be transmitted to sons. Although gr/gr frequencies vary with ethnicity, in populations of European descent, gr/gr deletions were observed in 3.7% of 515 men with non-obstructive azoospermia, 4.7% of 1179 men with severe oligospermia (sperm counts < 5 million/cc), and 0.6% of 804 men with normal sperm count <sup>10-17</sup>. Some published studies did not find statistically significant associations between gr/gr and low sperm count, but these studies did not include sufficient numbers of carefully phenotyped cases and controls. Indeed, a conservative meta analysis of studies in European populations shows a P value < 0.00001, with 123 gr/gr deletions among 3035 "infertile" men and 22 gr/gr deletions among 1393 men of "proven or presumed fertility," yielding an odds ratio of 2.6 <sup>16</sup>.

## HOW Y CHROMOSOME TESTING IS PERFORMED

Y chromosome deletions are detected using the polymerase chain reaction (PCR) with DNA primers which amplify regions known as sequence tagged-sites (STSs). When a region of the Y chromosome is deleted, the STSs it would have contained do not amplify, thereby indicating the deletion.

# Repromedix YCMD 3.0™: Y Chromosome Microdeletion Test

Clinician Information			Supporting Research						
Deletion	Observed Phenotype	Clinical Management	Azoospermia		Oligospermia		Normal		Refs
			N	Freq	N	Freq	N	Freq	
AZFa	Azoospermia	Establishes cause of azoo/oligospermia; no reported TESE success; consider sperm donation; genetic counseling	963	0.4%	602	0.0%	>1000	0.0%	18,19
AZFb (From P4 or P5 to proximal P1) AZFb+c (From P4 or P5 to distal P1)				1.5%					
AZFc (b2/b4)	Azoospermia or oligospermia	Establishes cause of azoo/oligospermia; TESE possible; consideration of PGD; genetic counseling	791	7.2%	492	6.5%	>1000	0.0%	6,19
Proximal Terminal centromere XG P4 or P5 P6, P7, P8 or KALP	Azoospermia	Establishes cause for azoospermia; no reported TESE success; discussion of risk of XO mosaicism in patient	889	3.0%	372	0.0%	N/A	0.0% <sup>a</sup>	15,19, 20
XX males	Azoospermia	Establishes cause of azoo/oligospermia; no reported TESE success; consider sperm donation; discussion of XX condition in patient; genetic counseling	b	1%	b	0.0%	>1000	0.0%	21
Distal Terminal IR2; P1; P2; P3; heterochromatin	Azoospermia or oligospermia	Establishes cause of azoo/oligospermia; TESE possible; consideration of PGD; genetic counseling	528	0.6%	372	0.0%	>200	0.0% <sup>c</sup>	15,19, 20
gr/gr (risk factor)	Azoospermia, oligospermia or normal	Establishes (partial) cause for reduced sperm count; possible increased testicular cancer risk; genetic counseling	515	3.7%	1179	4.6%	804	0.6%	8,10,
Miscellaneous (>5 deletions)	Oligospermia and unknown	Contact Repromedix for specific clinical information	b	~0.5%	b	~0.5%	b	b	15,23
b1/b3	Currently unknown but may change in future		377	0.8%	769	0.3%	507	0.2%	15,16
b2/b3			b	b	b	b	b	b	24,25
* TOTAL FREQUENCY OF CLINICALLY IMPORTANT DELETIONS IDENTIFIED BY REPROMEDIX				17.9% <sup>d</sup>		11.8% <sup>d</sup>			

FOOTNOTES: <sup>a</sup> Based on (P5 or P4)/p1 deletions, which remove a similar group of genes <sup>b</sup> Please see references <sup>c</sup> Unpublished data from MIT <sup>d</sup> b1/b3, b2/b3 not included in total

LEGEND  BEST AT REPROMEDIX: redesigned primer system has more confirmatory sites, increased consistency, and better position virtually eliminating high error rate found in other systems  ONLY AT REPROMEDIX: these deletions are only detected by Repromedix through a propriety system developed by MIT and Repromedix  ONLY AT REPROMEDIX: while currently of unknown clinical significance, may prove useful in the future

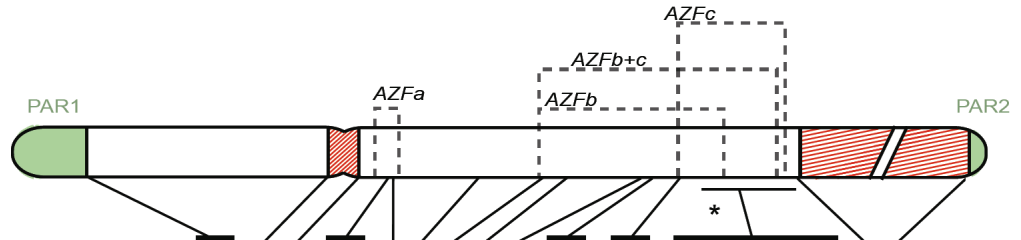
\* Repromedix identifies over 48% MORE DELETIONS of clinical importance than other laboratories



# Common Y Chromosome Microdeletions

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Map Position		ST1247	SY14	SY78	SY1251	SY1728	SY1714	SY1234	SY1276	SY1287	SY1573	SY627	SY1196	SY1197	SY1191	SY1192	SY1291	SY1189	SY1318	SY254	SY1206	SY1125	SY1201	SY1730	SY1575	Phenotype			
STS		PAR1 boundary**	SRY	centromere	centromere	USP9Y, exon3	USP9Y, exon46	DDX3Y (DBY)	Distal edge of P6	Distal edge of P4	JARID1D (SMCY)	RBMY1	u2 (center of P3)	u2 (center of P3)	u3 in AZFc	u3 in AZFc	red-gray boundary	red-gray boundary	DAZ	DAZ	yellow-green boundary	blue-gray boundary	AZFc distal boundary	PAR2 boundary**	X-linked positive control	Azoospermia	Azoospermia or Oligospermia	TESE possibly successful	
Deletion Detected		STS Result																							Phenotype				
AZFa																													N
AZFb (P5/proxP1)																													N
AZFb+c (P5/distP1)																													N
AZFc (b2/b4)																													Y
PROXIMAL TERMINAL	centromere																											N	
	XG																											N	
	P4 or P5																											N	
	P6, P7, P8 or KALP																											N	
XX males																												N	
DISTAL TERMINAL	IR2																											Y	
	P1																											Y	
	P2																											Y	
	P3																											Y	
	heterochromatin																											Y	
gr/gr																												Y	
b1/b3																												unknown	
b2/b3																												unknown	

\* Please see references 10 and 26 for details

\*\* PAR-pseudoautosomal region

### LEGEND

- Best at Repromedix
- Only at Repromedix
- Only at Repromedix but unknown clinical significance



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