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REPRODUCTIVE GENETICS INSTITUTE

INFORMATION PACKET

IN VITRO FERTILIZATION (IVF)

WITH

PREIMPLANTATION GENETIC DIAGNOSIS (PGD)

FOR SINGLE GENE DISORDERS (MUTATIONS)

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INTRODUCTION TO PREIMPLANTATION GENETIC DIAGNOSIS (PGD)

The Reproductive Genetics Institute (RGI) located in Chicago, Illinois, performs the most advanced procedures for the identification of genetic disorders before birth. Couples considering preimplantation genetic diagnosis (PGD) may already have a child with a genetic condition, may have terminated an affected pregnancy following prenatal diagnosis, may carry a balanced translocation (placing their pregnancies at a high risk for miscarriage or abnormal outcome), may have had a previous pregnancy that was chromosomally abnormal, or may be at increased risk for Down syndrome and other chromosome abnormalities (due to advancing maternal age). RGI can assist you in your family planning by offering genetic counseling regarding PGD and In Vitro Fertilization (IVF) (which is associated with this advanced procedure).

This packet will assist you in understanding PGD and IVF for single gene conditions. Some parts of this packet may not apply to you, depending on your specific concerns and circumstances for considering PGD.

PREIMPLANTATION GENETIC DIAGNOSIS (PGD)

The Reproductive Genetics Institute offers PGD to families at a high risk for producing offspring with genetic disorders. Performing genetic diagnosis prior to implantation may prevent the initiation of abnormal pregnancies and reduce the potential for the termination of affected fetuses diagnosed by prenatal testing.

For the past 19 years, more than 3,500 unaffected babies have been born following IVF with PGD for chromosomal and single gene disorders. We offer PGD for chromosomal abnormalities, such as Down syndrome (trisomy 21), trisomy 18 or trisomy 13. We also perform PGD for chromosomal translocations and over 200 single gene disorders.

At RGI, we specialize in PGD for single gene disorders including cystic fibrosis, Tay-Sachs Disease, fragile X syndrome, beta-thalassemia, hemophilia A, sickle cell disease, Duchenne muscular dystrophy and myotonic dystrophy to mention a few (see pages 4-9 for a complete listing of diseases). It is possible to do PGD for most genetic disorders with an identifiable gene/mutation.

PGD involves genetic testing of the oocytes and/or embryos obtained by undergoing In Vitro Fertilization (IVF). IVF is an assisted reproductive technology (ART) procedure in which fertilization of the egg occurs outside of the body in a controlled setting. The oocyte (egg) is removed from the woman's ovary and is placed with the male's sperm. If the sperm fertilizes the egg, the fertilized egg (zygote) begins to divide. Several techniques can be utilized in order to determine the genetic make-up of the embryo, depending on whether the diagnosis is for aneuploidies (extra/missing chromosomes), translocations, or single gene disorders. The genetic status of the embryo(s) can be determined before the embryo(s) is/are transferred into the uterus. This innovative technology is a valuable alternative available to couples who are at risk for a genetic condition. At this time, prenatal diagnosis by chorionic villus sampling (CVS) or amniocentesis is still recommended for reassurance and confirmation of PGD results.

The following procedures are necessary when undergoing PGD and IVF:

1. Ovulation Induction
2. Oocyte Aspiration
3. Fertilization and Embryo Culture
4. Polar body removal and/or blastomere biopsy
5. Genetic testing
6. Embryo transfer and implantation
7. Embryo Cryopreservation (if requested by patient)
8. Confirmation studies by CVS or amniocentesis (recommended but not required)

If you live outside of Illinois, it is possible for us to work with your local Reproductive Specialist for part (or all) of your cycle in an effort to reduce or eliminate the need for you to travel to Chicago.

**RGI HAS DESIGNED PGD SYSTEMS FOR THE FOLLOWING
SINGLE GENE DISORDERS AS OF 10/2009**

PLEASE NOTE: WE ARE ABLE TO OFFER PGD FOR MOST GENETIC CONDITIONS AS LONG AS THE GENE/ MUTATION(S) ARE KNOWN. IF YOUR DISEASE IS NOT ON THIS LIST PLEASE CONTACT AN RGI GENETIC COUNSELOR TO SEE IF PGD IS A FEASIBLE OPTION FOR YOU

Disease	Gene
ACHONDROPLASIA (ACH)	FGFR3
ACYL-CoA DEHYDROGENASE, MEDIUM-CHAIN, DEFICIENCY	ACADM
ACYL-CoA DEHYDROGENASE, VERY LONG-CHAIN, DEFICIENCY	ACADVL
ADENOSINE DEAMINASE DEFICIENCY (ADA)	ADA
ADRENOLEUKODYSTROPHY (ALD)	ABCD1
AGAMMAGLOBULINEMIA, BRUTON; X-LINKED, TYPE I	BTK
AICARDI-GOUTIERES SYDNROME 1 (AGS1)	TREX1
ALBINISM, OCULAR, TYPE I	OA1
ALOPECIA UNIVERSALIS CONGENITA (ALUNC)	HR
ALPERS DIFFUSE DEGENERATION OF CEREBRAL GRAY MATTER WITH HEPATIC CIRRHOSIS	POLG
ALPHA 1 ANTITRYPSIN DEFICIENCY (AAT)	SERPINA1
ALPORT SYNDROME, X-LINKED (ATS)	AMMECR1
ALZHEIMER DISEASE, EARLY-ONSET FAMILIAL	APP
AMYLOIDOSIS I, HEREDITARY NEUROPATHIC	TTR
AMYOTROPHIC LATERAL SCLEROSIS 1 (ALS1)	SOD1
ANDROGEN RECEPTOR (TESTICULAR FEMINIZATION)	AR
ANEUPLOIDIES BY STR GENOTYPING	
ANGIOEDEMA, HEREDITARY (HAE)	SERPING1
ARGININOSUCCINIC ACIDURIA	ASL
ATAXIA-TELANGIECTASIA (AT)	ATM
BASAL CELL NEVUS SYNDROME; BCNS (GORLIN)	PTCH
BETA-HYDROXYISOBUTYRYL CoA DEACYLASE, DEFICIENCY OF	HIBCH
BLEPHAROPHIMOSIS, PTOSIS, AND EPICANTHUS INVERSUS (BPES)	FOXL2
BLOOD GROUP--KELL-CELLANO SYSTEM	KEL
BRACHYDACTYLY, TYPE B1 (BDB1)	ROR2
BRAIN TUMOR, POSTERIOR FOSSA OF INFANCY, FAMILIAL	SMARCB1
BREAST-OVARIAN CANCER, FAMILIAL	BRCA1
BREAST-OVARIAN CANCER, FAMILIAL	BRCA2
CANAVAN DISEASE	ASPA

CARDIOENCEPHALOMYOPATHY, FATAL INFANTILE, DUE TO CYTOCHROME c OXIDASE DEFICIENCY	SCO2
CARDIOMYOPATHY, FAMILIAL HYPERTROPHIC, 4 (CMH4)	MYBPC3
CEROID LIPOFUSCINOSIS, NEURONAL 2, LATE INFANTILE; CLN2	CLN2
CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2E	NEFL
CHARCOT-MARIE-TOOTH DISEASE, DEMYELINATING, TYPE 1A (CMT1A)	PMP22
CHARCOT-MARIE-TOOTH DISEASE, DEMYELINATING, TYPE 1B (CMT1B)	MPZ
CHARCOT-MARIE-TOOTH DISEASE, X-LINKED, 1; CMTX1	GJB1
CHOLESTASIS, PROGRESSIVE FAMILIAL INTRAHEPATIC 2	ABCB11
CHONDRODYSPLASIA PUNCTATA 1, X-LINKED RECESSIVE (CDPX1)	ARSE
CHOROIDEREMIA (CHM)	CHM
CITRULLINEMIA, CLASSIC	ASS
COHEN SYNDROME (COH1)	VPS13B
COLLAGEN, TYPE IV, ALPHA-5	COL4A5
CONGENITAL ADRENAL HYPERPLASIA (CAH)	CYP21A2
CORNEAL DYSTROPHY, AVELLINO TYPE (CDA)	TGFB1
CRANIOFACIAL DYSOSTOSIS, TYPE I (CFD1)	FGFR2
CURRARINO SYNDROME	HLXB9
CUTIS LAXA, AUTOSOMAL RECESSIVE, TYPE I	FBLN4
CYSTIC FIBROSIS (CF)	CFTR
CYSTINOSIS, NEPHROPATHIC (CTNS)	CTNS
DARIER-WHITE DISEASE (DAR)	ATP2A2
DEAFNESS, NEUROSENSORY, AUTOSOMAL RECESSIVE 1 (DFNB1)	GJB2
DIAMOND-BLACKFAN ANEMIA (DBA)	RPS19
DONOHUE SYNDROME	INSR
ECTODERMAL DYSPLASIA 1, ANHIDROTIC	ED1
ECTODERMAL DYSPLASIA, ANHIDROTIC	EDAR
ECTRODACTYLY, ECTODERMAL DYSPLASIA, AND CLEFT LIP/PALATE SYNDROME 1 (EEC1)	p63
EHLERS-DANLOS SYNDROME, TYPE VI	PLOD1
EMERY-DREIFUSS MUSCULAR DYSTROPHY, AUTOSOMAL RECESSIVE; EDMD3	LMNA
EMERY-DREIFUSS MUSCULAR DYSTROPHY, X-LINKED (EDMD)	EMD
EPIDERMOLYSIS BULLOSA DYSTROPHICA, PASINI TYPE	COL7A1
EPIDERMOLYSIS BULLOSA LETALIS	LAMB3
EPIDERMOLYSIS BULLOSA SIMPLEX WITH PYLORIC ATRESIA	PLEC1
EPIPHYSEAL DYSPLASIA, MULTIPLE, 1 (EDM1)	COMP
EXOSTOSES, MULTIPLE, TYPE I	EXT1

FABRY DISEASE	GLA
FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY 1A (FSHMD1A)	FRG1
FAMILIAL ADENOMATOSIS POLYPOSIS (FAP)	APC
FAMILIAL MEDITERRANEAN FEVER GENE	MEFV
FANCONI ANEMIA, COMPLEMENTATION GROUP A	FANCA
FANCONI ANEMIA, COMPLEMENTATION GROUP C	FANCC
FANCONI ANEMIA, COMPLEMENTATION GROUP E	FANCE
FANCONI ANEMIA, COMPLEMENTATION GROUP F	FANCF
FANCONI ANEMIA, COMPLEMENTATION GROUP G	FANCG
FANCONI ANEMIA, COMPLEMENTATION GROUP I	FANCI
FANCONI ANEMIA, COMPLEMENTATION GROUP J	BRIP1
FRAGILE SITE MENTAL RETARDATION 1	FMR1
FRAGILE SITE, FOLIC ACID TYPE, RARE, FRA(X)(q28); (FRAXE)	FMR2
FRIEDREICH ATAXIA 1 (FRDA)	FRDA
GALACTOSEMIA	GALT
GANGLIOSIDOSIS, GENERALIZED GM1, TYPE I	GLB1
GAUCHER DISEASE, TYPE I	GBA
GERODERMA OSTEODYSPLASTICUM (GO)	SCYL1BP1
GLAUCOMA 3, PRIMARY CONGENITAL, A (GLC3A)	CYP1B1
GLUCOSE TRANSPORT DEFECT; BLOOD-BRAIN BARRIER	SLC2A1
GLUCOSE-6-PHOSPHATE DEHYDROGENASE	G9PD
GLUTARIC ACIDEMIA 1	GCDH
GLYCINE ENCEPHALOPATHY (GCE)	GLDC
GLYCOGEN STORAGE DISEASE I	G6PC
GLYCOGEN STORAGE DISEASE II	GAA
GLYCOGEN STORAGE DISEASE TYPE VI	PYGL
GRANULOMATOUS DISEASE, CHRONIC, X-LINKED (CGD)	CYBB
HEMOGLOBIN--ALPHA LOCUS 1	HBA1
HEMOGLOBIN--ALPHA LOCUS 2	HBA2
HEMOGLOBIN--BETA LOCUS	HBB
HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS, FAMILIAL, 2	PRF1
HEMOPHILIA A	F8
HEMOPHILIA B	F9
HEREDITARY NONPOLYPOSIS COLORECTAL CANCER (HNPCC)	MSH2
HEREDITARY NONPOLYPOSIS COLORECTAL CANCER (HNPCC)	MLH1
HLA MATCHING GENOTYPING	
HOLOPROSENCEPHALY	SHH

HOMOCYSTINURIA DUE TO DEFICIENCY OF N(5,10)-METHYLENETETRAHYDROFOLATE REDUCTASE ACTIVITY	MTHFR
HOYERAAL-HREIDARSSON SYNDROME (HHS)	DKC1
HUNTINGTON DISEASE (HD)	HTT
HYDROCEPHALUS, X-LINKED	L1CAM
HYPERINSULINEMIC HYPOGLYCEMIA, FAMILIAL, 1 (HHF1)	ABCC8
HYPOMAGNESEMIA, RENAL, WITH OCULAR INVOLVEMENT	CLDN16
HYPOPHOSPHATASIA, INFANTILE	ALPL
HYPOPHOSPHATEMIC RICKETS, X-LINKED DOMINANT	PHEX
ICHTHYOSIS FOLLICULARIS, ATRICHIA, AND PHOTOPHOBIA SYNDROME	MBTPS2
ICHTHYOSIS, LAMELLAR, 1 (LI1)	TGM1
ICHTHYOSIS, LAMELLAR, 2 (LI2)	ABCA12
IMMUNODEFICIENCY WITH HYPER-IgM, TYPE 1 (HIGM1)	CD40LG
IMMUNODYSREGULATION, POLYENDOCRINOPATHY, AND ENTEROPATHY, X-LINKED (IPEX)	FOXP3
INCONTINENTIA PIGMENTI (IP)	IKBKG
ISOVALERIC ACIDEMIA (IVA)	IVD
KRABBE DISEASE	GALC
LEIGH SYNDROME (LS)	SURF1
LEUKOENCEPHALOPATHY WITH VANISHING WHITE MATTER (VWM)	EIF2B2
LEUKOENCEPHALOPATHY WITH VANISHING WHITE MATTER (VWM)	EIF2B4
LI-FRAUMENI SYNDROME 1 (LFS1)	TP53
LOEYS-DIETZ SYNDROME (LDS)	TGFBR2
LONG-CHAIN 3-HYDROXYACYL-CoA DEHYDROGENASE DEFICIENCY	HADHA
MACHADO-JOSEPH DISEASE (MJD)	ATX3
MARFAN SYNDROME (MFS)	FBN1
METACHROMATIC LUEKODYSTROPY	ARSA
METAPHYSEAL CHONDRODYSPLASIA, SCHMID TYPE (MCDS)	COL10A1
MICROCORIA-CONGENITAL NEPHROSIS SYNDROME	LAMB2
MICROTUBULE-ASSOCIATED PROTEIN TAU	MAPT
MIGRAINE, FAMILIAL HEMIPLEGIC, 1 (FHM1)	CACNA1A
MORQUIO SYNDROME, NONKERATOSULFATE-EXCRETING TYPE; MUCOPOLYSACCHARIDOSIS TYPE IVA	GALNS
MUCOPOLYSACCHARIDOSIS TYPE I (HURLER)	IDUA
MUCOPOLYSACCHARIDOSIS TYPE II (HUNTER)	IDS
MUCOPOLYSACCHARIDOSIS TYPE VI (MAROTEAUX-LAMY)	ARSB
MULTIPLE ACYL-CoA DEHYDROGENASE DEFICIENCY (MADD)	ETFA
MULTIPLE ENDOCRINE NEOPLASIA, TYPE I	MEN1

MULTIPLE ENDOCRINE NEOPLASIA, TYPE IIA	RET
MUSCULAR DYSTROPHY, BECKER TYPE (BMD)	DMD
MUSCULAR DYSTROPHY, DUCHENNE TYPE (DMD)	DMD
MYOPATHY, MYOFIBRILLAR, DESMIN-RELATED	DES
MYOTONIC DYSTROPHY	DMPK
MYOTUBULAR MYOPATHY 1	MTM1
N-ACETYLGLUTAMATE SYNTHASE DEFICIENCY	NAGS
NEPHROSIS 1, CONGENITAL, FINNISH TYPE	NPHS1
NEUROFIBROMATOSIS, TYPE I	NF1
NEUROFIBROMATOSIS, TYPE II;	NF2
NEUROPATHY, HEREDITARY SENSORY AND AUTONOMIC, TYPE I (HSAN1)	SPTLC1
NEUROPATHY, HEREDITARY SENSORY AND AUTONOMIC, TYPE III (HSAN3)	IKBKAP
NIEMANN-PICK DISEASE, TYPE A	SMPD1
NOONAN SYNDROME 1 (NS1)	PTPN11
NORRIE DISEASE	NDP
OCULOCUTANEOUS ALBINISM, TYPE I (OCA1)	TYR
OCULOCUTANEOUS ALBINISM, TYPE II (OCA2)	OCA2
OMENN SYNDROME	RAG1
OPTIC ATROPHY 1	OPA1
ORNITHINE TRANSCARBAMYLASE DEFICIENCY	OTC
OSTEOGENESIS IMPERFECTA CONGENITA (OI)	COL1A1
OSTEOGENESIS IMPERFECTA CONGENITA (OI)	COL1A2
OSTEOPETROSIS, AUTOSOMAL RECESSIVE	TCIRG1
PANCREATITIS, HEREDITARY (PCTT)	PRSS1
PELIZAEUS-MERZBACHER-LIKE DISEASE (PMLD)	PLP1
PEUTZ-JEGHERS SYNDROME (PJS)	STK11
PHENYLKETONURIA	PAH
POLYCYSTIC KIDNEY DISEASE 1	PKD1
POLYCYSTIC KIDNEY DISEASE 2	PKD2
POLYCYSTIC KIDNEY DISEASE, AUTOSOMAL RECESSIVE (ARPKD)	PKHD1
POPLITEAL PTERYGIUM SYNDROME; PPS	IRF6
PROPIONIC ACIDEMIA	PCCA
PROPIONIC ACIDEMIA	PCCB
PYRIDOXAMINE 5-PRIME-PHOSPHATE OXIDASE DEFICIENCY	PNPO
RETINITIS PIGMENTOSA	RHO
RETINITIS PIGMENTOSA 3 (RP3)	RPGR
RETINOBLASTOMA	RB1

RETT SYNDROME (RTT)	MECP2
RHESUS BLOOD GROUP, CcEe ANTIGENS	RHCE
RHESUS BLOOD GROUP, D ANTIGEN	RHD
SANDHOFF DISEASE	HEXB
SICKLE CELL ANEMIA (HbC; HbS)	HBB
SMITH-LEMLI-OPITZ SYNDROME (SLOS)	DHCR7
SOTOS SYNDROME	NSD1
SPINAL AND BULBAR MUSCULAR ATROPHY (KENNEDY DISEASE)	AR
SPINAL MUSCULAR ATROPHY, TYPE I (SMA1)	SMN1
SPINOCEREBELLAR ATAXIA 1 (SCA1)	ATXN1
SPINOCEREBELLAR ATAXIA 2 (SCA2)	ATX2
SPINOCEREBELLAR ATAXIA 6 (SCA6)	CACNA1A
SPINOCEREBELLAR ATAXIA 7 (SCA7)	SCA7
STICKLER SYNDROME, TYPE I (STL1)	COL2A1
STICKLER SYNDROME, TYPE II (STL2)	COL11A1
SUCCINIC SEMIALDEHYDE DEHYDROGENASE DEFICIENCY	ALDH5A1
SURFACTANT METABOLISM DYSFUNCTION, PULMONARY, 3 (SMDP3)	ABCA3
SYMPHALANGISM, PROXIMAL (SYM1)	NOG
TAY-SACHS DISEASE (TSD)	HEXA
THROMBOTIC THROMBOCYTOPENIC PURPURA, CONGENITAL (TTP)	ADAMTS13
TORSION DYSTONIA 1, AUTOSOMAL DOMINANT (DYT1)	TOR1A
TREACHER COLLINS-FRANCESCHETTI SYNDROME	TCOF
TUBEROUS SCLEROSIS TYPE 1	TSC1
TUBEROUS SCLEROSIS TYPE 2	TSC2
TYROSINEMIA, TYPE I	FAH
ULNAR-MAMMARY SYNDROME (UMS)	TBX3
VON HIPPEL-LINDAU SYNDROME	VHL
WISKOTT-ALDRICH SYNDROME	WAS
WOLMAN DISEASE	LIPA
ZELLWEGER SYNDROME (ZS)	PEX1
ZELLWEGER SYNDROME (ZS)	PXMP3

** We have the ability to offer PGD for most conditions where a molecular diagnosis has been established. Please contact a Genetic Counselor at RGI for more details. We can be reached by phone at: 773-472-4900, fax: 773-871-5221, Email: rgiworld@gmail.com.

OVULATION INDUCTION

Ovulation normally involves the release of a single mature egg from its follicle in the ovary. In the IVF process, multiple mature eggs are retrieved before they are ovulated. Medication is used during a woman's cycle in order to stimulate the eggs to mature simultaneously. The large majority of the medications used during an IVF cycle are administered by injection. Usually, there are three groups of medications used. The first group consists of medications that stimulate the ovary to produce more than one mature egg. These include Gonal F, Repronex, Follistim, and Pergonal.

In order to be able to collect the eggs, other medications are used to prevent spontaneous ovulation to occur. These medications include Lupron, Cetrotide and Antagon.

A third medication, human chorionic gonadotropin (hCG), is administered to trigger final oocyte maturation before the egg is retrieved. Progesterone may also be administered before egg retrieval to maintain a thick endometrial lining in order to promote implantation. Ovulation normally occurs 38 hours after hCG is administered; therefore, egg retrieval is timed 34-38 hours after the injection of hCG.

Ultrasound and blood tests carefully monitor the effects of the maturing follicles. The blood tests measure the amount of estradiol (E2) in the blood. Because follicles secrete E2, levels in the blood will show the follicles' responses to the medications. Vaginal ultrasounds show the number, location, and size of the follicles. The ultrasounds and blood tests will determine whether the follicles are ready to be retrieved. If the follicles are not well stimulated or the number of follicles is too small for the purpose of PGD, the cycle may be cancelled and a new cycle begun with a different dosage of medication.

Hyperstimulation Assessment:

One of the risks of taking fertility medications is the possibility of ovarian hyperstimulation syndrome (OHSS). Severe OHSS may occur in less than 1% of cycles. Monitoring throughout the cycle can minimize the number of follicles and the level of estradiol produced by the follicles. If on the day that you are given hCG, your estradiol is between 3,000-5,000 pg/ml your eggs may need to be retrieved, fertilized, and the resulting embryos frozen, otherwise, there is a risk of complications due to hyperstimulation if you become pregnant this cycle. The embryos may be frozen and transferred in a different cycle. If the estradiol is more than 5,000 pg/ml, prior to your egg retrieval, this cycle may even need to be cancelled (no egg retrieval), and medications adjusted the next cycle.

OOCYTES ASPIRATION (EGG RETRIEVAL)

A small needle inserted in a guide attached to an ultrasonic probe is used to perform the aspiration of the follicle. Using ultrasound to guide the needle path, the physician directs the needle through the vaginal wall into the ovarian follicles. The needle is connected to a suction pump and the fluid from each accessible follicle within the ovary is aspirated. The patient is usually awake but mildly sedated during this procedure by administering intravenous Demerol or Versed ("twilight sleep"). The patient can be put under general anesthesia for an additional cost.

The retrieved eggs are cultured for approximately 6 to 20 hours depending on maturity before being exposed to sperm.

FERTILIZATION AND EMBRYO CULTURE

The laboratory testing procedures take place in a special laboratory in which all conditions are sterile. The egg cell prior to fertilization divides into two unequal cells. The larger cell is the mature egg that will be fertilized. The smaller cell (called a polar body) can be removed (polar body removal) and tested for its genetic composition (see below).

A semen sample is provided to the laboratory on the day of the egg retrieval. The semen sample is then processed in order to obtain an optimal sperm sample for fertilization. When the sperm sample is normal and PGD is not planned, then regular in vitro insemination of the eggs is possible. Otherwise, a single sperm is injected into the egg by a procedure known as intracytoplasmic sperm injection or **ICSI**. At this time, a second polar body is released from the egg. The eggs will be fertilized using ICSI to maximize the rate of fertilization and to monitor the exact timing of polar body release. Occasionally, fertilization does not occur, or occurs abnormally (which happens to fertile couples as well).

After fertilization has taken place, the embryo is transferred to a special growth medium. The culture dishes are maintained in an incubator where the atmosphere, humidity, and temperature are carefully monitored and controlled.

POLAR BODY REMOVAL

As indicated above, the first polar body produced from the division of the egg can be removed and tested for its chromosome complement or to identify whether it contains the abnormal gene of concern. Upon penetration of the egg by the sperm (fertilization), but prior to the joining of the sperm's genetic material with the egg's genetic material, the egg undergoes another cell division, producing two unequally sized cells. The genetic material from the larger cell will join with the sperm's genetic material to create the pre-embryo, whereas the smaller cell is called the second polar body. Polar bodies have no known function. They are simply "by-products" of the egg's division. Once implantation occurs, the polar bodies disintegrate and are not part of the developing fetus. By testing the first and second polar bodies, the maternal genetic contribution to the resultant embryo can be determined. Removal and genetic analysis of the polar bodies occurs on the first and second day after aspiration. If one or both polar bodies fail(s) to provide a conclusive result, it may be necessary to perform a blastomere biopsy (embryo biopsy) for further genetic analysis.

EMBRYO (BLASTOMERE) BIOPSY

On the day of egg retrieval, the egg is typically be fertilized by ICSI. Following fertilization, the zygote begins to divide. On the third day following the egg retrieval, the embryo is at the blastomere stage (consisting of 6-10 cells), and a cell may be carefully removed (blastomere/embryo biopsy) for genetic analysis. After removal of the cell(s) from the

blastomere, the developing embryo is placed back into the culture dish and genetic analysis is performed separately on the removed cell(s). The blastomere has genetic information from both the egg and the sperm.

At this early point of embryo development, as far as we know, all of the cells are equivalent and thus, removal of a cell from the embryo at this stage does not remove anything critical for normal development. The embryo compensates for the removed cell and should continue to divide following blastomere biopsy.

The techniques related to PGD are not 100% accurate and RGI encourages all patients who have undergone PGD to have prenatal testing, as this is still the current standard of care.

EMBRYO TRANSFER AND IMPLANTATION

Once an embryo is predicted to be free from the genetic disease for which testing was performed, the embryo will be recommended for transfer. The patient and their IVF physician will determine the number of embryos that are transferred for one IVF cycle. The embryos may be transferred:

1. THREE DAYS after egg retrieval. This is possible if the genetic analysis is complete and conclusive by polar body analysis alone. OR
2. FIVE DAYS after egg retrieval, at the blastocyst stage. This is required for cases involving blastomere (embryo cell) biopsy.

Embryo transfer is typically a brief procedure accomplished by inserting a catheter (preloaded with embryos) into the uterine cavity. This procedure is often performed under ultrasound guidance and is generally no more uncomfortable than a pap smear. Although a quick procedure, it is necessary to remain at the IVF center in a reclined position for approximately 20-30 minutes after transfer. The embryos will initially be free floating and reclining should facilitate them implanting into the thick uterine lining. Traveling should be postponed for at least a day and restricted to being the passenger in a car.

Patients are routinely prescribed progesterone (injections, cream, or suppositories) from the day they are given hCG until the day of their pregnancy test. The pregnancy test is performed ten to twelve days after the embryo transfer. It can be done at the center or at your doctor's office, but should be a blood test (not a home pregnancy test). If the pregnancy test is positive, your IVF physician will instruct you to continue taking progesterone for approximately 4-6 weeks, as this is important in maintaining a thick uterine lining.

EMBRYO CRYOPRESERVATION

If extra embryos are available following egg retrieval, fertilization, genetic analysis, and transfer, patients will be counseled regarding the remaining embryos available for freezing. Patients will decide which embryos they wish to have frozen and transferred in a future cycle. The cost for a frozen embryo transfer (FET) cycle will vary, however is significantly less than another IVF/PGD cycle.

PREIMPLANTATION DIAGNOSIS OF SINGLE GENE DISORDERS

Currently, PGD for single gene disorders can be accomplished by polar body removal or blastomere biopsy. The method that is used is determined on a case-by-case basis. Our genetic counselors can assist you in determining what type of analysis would be optimal in your scenario. PGD is used to select for embryos that do not have a specific genetic disease by testing cells for a known genetic mutation. Additionally, we test for specific linked markers that are inherited along with the gene to enhance diagnostic accuracy.

Patients and PGD centers worldwide are concerned about the possibility of misdiagnosis, which can occur as a result of failure of allele specific amplification, or **allele dropout (ADO)**. Basically, this is the failure of one of the genes (allele) to show up in the analysis (it “drops out” of the picture.) ADO is of concern primarily in blastomere biopsy when each parent carries a different mutation for a recessive condition. To minimize the potential for diagnostic error by PGD, it is preferable to offer polar body removal or to perform a combined analysis of the specific mutation and tightly linked genetic markers. This dual amplification allows for higher accuracy and for the detection of ADO, thus reducing the risk for misdiagnosis.

RGI physicians have already performed over 1,800 clinical cycles involving preimplantation diagnosis for cystic fibrosis, Tay-Sachs disease, hemophilia A, alpha-1-antitrypsin deficiency, retinitis pigmentosa and sickle cell disease, and LCHAD deficiency, to name a few. These cycles have resulted in delivered or ongoing pregnancies confirmed to be unaffected by CVS, amniocentesis, or genetic testing following delivery.

Polymerase Chain Reaction (PCR)

Polymerase chain reaction (PCR) is a technique that is used to produce large amounts of specific DNA sequences from a small amount of DNA so that further analysis can be performed. The process begins with a sample of an individual's DNA. The DNA is denatured into single strands. Short single-stranded primers pair with the nucleotides adjacent to the region to be amplified. The primers are synthetic but are complementary to the original nucleotide sequence. Then, enzymes and nucleotides for DNA synthesis are added and the primers are extended, forming a double stranded DNA molecule that is identical to the original DNA strand. This process is repeated to obtain more copies of the DNA. Repeated cycles can amplify the original DNA sequence by up to a billion times.

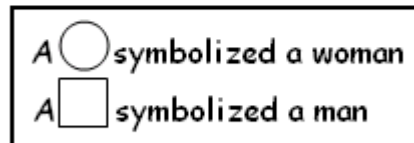
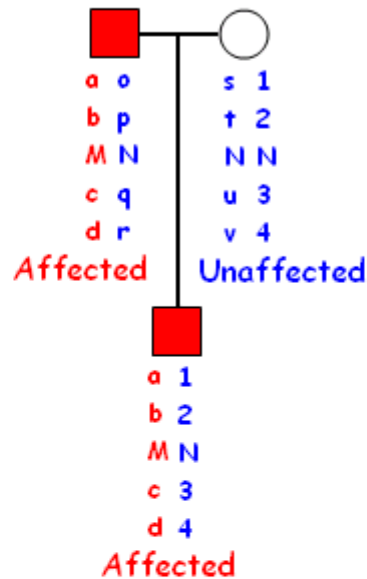
Given the small amount of DNA in the polar bodies or blastomere, this is a valuable technique that allows us to perform analysis of that DNA and make a diagnosis.

Linkage Analysis

This is a method of determining if two or more genes have an increased probability of being inherited together. If genes are considered to be “linked”, the genes are present on the same chromosome region and have a high probability of being inherited together. In a genetic map, genes are arranged in a linear order; the distance between any two genes is measured by how frequently crossing over takes place between them. The smaller the distance between the genes, the lower the probability that crossing over will occur between the genes and therefore there is a higher probability that the genes will remain together throughout meiosis (cell division) and become inherited as a unit.

Linkage analysis is used to further improve the accuracy of PGD by looking for the inheritance of the linked markers in addition to the specific genetic mutation. Linkage analysis is attempted in all cases to decrease the possibility of undetected ADO. The number of linked markers used is different for each family and cannot be determined until we have completed our "PGD setup".

How linked markers are inherited together



Key: **M** stands for the mutation. **N** stands for a normal sequence. The remaining numbers and letters stand for genetic sequences that are unique to that specific location in the chromosome (this is part of normal human variation). Linkage is established by analyzing the DNA of at least two members of a family known to be affected with the disease/mutation.

PROTOCOL FOR EVALUATION AND PARTICIPATION IN PROGRAM

1. After reviewing this information packet, please contact one of our genetic counselors/PGD coordinators for information regarding our center's services by calling (773) 472-4900 or email them at rgiworld@gmail.com. They will be able to answer questions regarding our center and what test results or paperwork is required. They will also be able to give you information regarding the costs for PGD and/or IVF.
2. If you are located in the Chicago area and want to do both the PGD and the IVF in one place, our genetic counselors will place you in contact with one of our Reproductive Specialists.
3. After talking with a genetic counselor, you will be sent the necessary paperwork and DNA collection kits required for PGD. Once we have all the DNA samples, the necessary consents and required payment, we will start your PGD setup. The development of the setup (based on mutation and/or linked markers) will take about 4-8 weeks to complete. Once the PGD setup is complete you will be free to start your IVF medications. Please note: The consent forms needs to be signed, notarized and returned (original copy, please, no faxed copies) along with the payment for the PGD. Your doctor's office will complete the Requisition form and fax it to us once you have cycling dates. **All paperwork and payment must be received prior to starting medications.**
4. You have the option of undergoing IVF at our center OR at another center local to you. If your chosen IVF center cannot perform the required biopsies for your case, we may be able to send one of our experienced embryologists to your center to perform the biopsies for your case*.

*If you choose to pursue IVF outside of RGI, and need an RGI embryologist to travel to your center for the biopsies it is important to ensure that your local IVF center has the appropriate equipment required by our staff. If your local IVF center does not have the required equipment and/or biopsy experience, you may prefer to come to RGI for your IVF cycle OR transport your embryos (in a portable incubator) to our center for the biopsy and testing.

If you would like to pursue your IVF cycle at RGI in Chicago, the steps are as follows:

- a) Your genetic counselor will put you in touch with one of our Reproductive Specialists, to arrange a new patient consultation. This consult can be done over the phone or in person. There is a non-refundable fee for this consultation.
- b) Our Reproductive Specialist will send you a list of required pre-IVF laboratory tests. These tests must have been performed in the past 6-12 months, and can be arranged through our office or your local OBGYN or IVF center.
- c) Our Reproductive Specialist will be responsible for reviewing all test results and for choosing the medication protocol for ovarian stimulation.

- d) You must have a center to monitor you while on IVF medications. This monitoring can be done through our office or through a center closer to your home. The monitoring results (blood test and ultrasound results) must be sent to our IVF center for review. Please provide your IVF Coordinator the contact information for your monitoring center; so we can properly monitor your cycle's progress.
- e) You may arrive in Chicago before or during ovarian stimulation and complete the monitoring here, or you may wait and arrive one day before the Egg Retrieval. We need you and your male partner (or his frozen sperm sample) to be in Chicago on the day of egg retrieval. You may expect embryo transfer (ET) to be performed 5 days after the egg retrieval. You may plan your return trip for the following day.

If you would prefer to undergo your **IVF cycle in a center in your area**, these steps should be followed:

- a) Contact one of our genetic counselors to determine whether there is a center in your area with which we have already established a working relationship. If so, we may refer you to this center for your IVF cycle.
- b) If there are no centers in your area with which we have a working relationship, we will assist you in locating such a center and contacting them regarding their willingness to establish a relationship with RGI for the purposes of offering PGD. Once a site is selected, this information should be shared with your RGI genetic counselor, including contact information.
- c) If your entire IVF cycle will be completed in your area and you are working with an IVF center that is experienced in performing its own biopsies, an RGI embryologist will NOT be involved. **You will only need to make payment to RGI for the PGD.**
- d) If your entire IVF cycle will be completed in your area and you are working with an IVF center that **cannot** perform their own biopsies, your case will require one of our embryologists to travel to your area to perform the removal of the polar bodies and/or blastomeres for the purpose of the PGD. **The PGD costs as well as the costs associated with the travel of this individual and the biopsy fee will be incurred by you, and you will be responsible for paying these fees prior to starting medications.**
- e) If you are working with an outside IVF center and would like us to perform the biopsies on your embryos, you (or someone on your behalf) may wish to travel to Chicago with your embryos in a portable incubator. **You will be responsible for the PGD costs as well as the biopsy and incubator fees.**
- f) You should contact one of our genetic counselors when you have a written protocol of how your cycle is expected to be conducted (many centers use a "calendar" format). Specifically, we must know the date Lupron is begun and when stimulation is started. Additionally, we will need updates, either from yourself or the nurse coordinator in charge of your case, on how your IVF cycle is progressing. **Finally, it is critical to make contact with our center once you have been instructed on when to administer the hCG shot (or trigger shot) so that travel plans can be finalized and our lab can be ready for your case.**

PAYMENTS

- a) Regarding insurance coverage: Please contact your insurance company regarding the coverage for IVF medications, IVF treatment, PGD biopsy procedures and/or PGD. Even if your medical insurance covers one or more of the above, we require that all payment be made in full prior to beginning a cycle. Therefore, it is your responsibility to pay these costs up front. RGI is willing to submit claims to your insurance company and reimburse any money owed to you.
- b) You are responsible for all fertility medication costs. You should check with your insurance regarding possible coverage of these medications. A prescription will be provided to you by your Reproductive Specialist for all needed medications and it can be arranged that your medications are shipped directly to you.
- c) Payment for your IVF/PGD cycle is due once you are on stimulation prior to your egg retrieval. We accept Visa, MasterCard, American Express, personal check or wire transfer.

We have provided the following information as an example of what is involved with one IVF cycle. The timing of IVF cycles and the medications taken during an IVF cycle will vary from patient to patient. Your Reproductive Specialist will prescribe your IVF medications.

Prior to starting your IVF cycle, it is common for your physician to put you on birth control pills for few weeks in order to regulate your menstrual cycle.

The first day that you begin your menstrual cycle is commonly referred to as Day 1. Twenty-one days after Day 1, you will start taking a medication called Lupron. Within 10-14 days after being on Lupron, you will get your period. You will then have a baseline ultrasound examination and will start taking stimulation medications within a few days.

Stimulation involves lowering your dose of Lupron and starting to take stimulation medications (ie. Gonal-F, Repronex, Follistim, Pergonal). These medications will be taken for approximately 9-12 days.

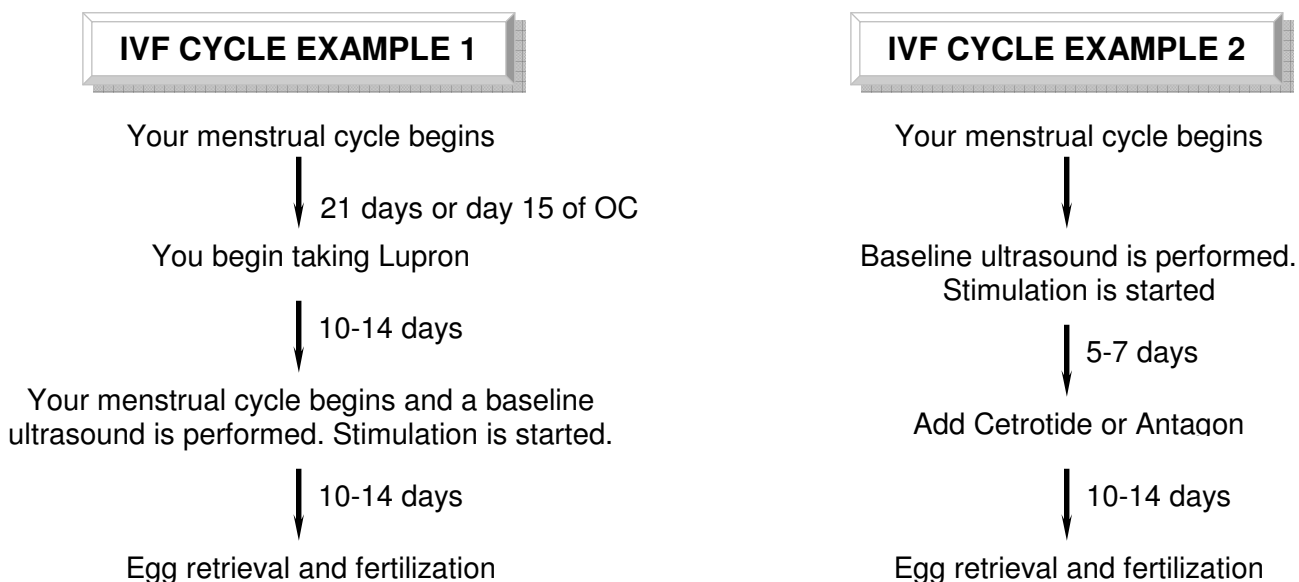
If Lupron will not be used, but Cetrotide or Antagon, then you will start the stimulation medication first (on day 2 or 3 of cycle) and only after 5-7 days this newer medication will be added.

While you are undergoing stimulation, you will be monitored by blood tests and ultrasounds. During the ultrasounds, the number and size of follicles will be monitored.

When some of the follicles reach a size of 18-20 mm, you will be administered hCG (human chorionic gonadotropin). You will stop taking Lupron and the stimulation medications.

Approximately 35 hours after hCG is administered, the eggs will be retrieved. Three to five days after egg retrieval, embryo transfer will occur.

* Your IVF cycle may vary depending on your age and response to the IVF medications.



CONFIRMATION STUDIES OF GENETIC TESTING

We recommend that all patients undergo prenatal diagnosis (CVS, amniocentesis) following preimplantation genetic diagnosis for the purpose of reassurance and confirmation. We recommend that confirmation testing be done by an independent, outside, clinical laboratory whenever possible. However, we do offer confirmation testing on all PGD pregnancies/ babies on a research-basis only. Our genetic counselors can help you coordinate this testing, if needed.

The two common methods of diagnostic prenatal testing —chorionic villus sampling (CVS) and amniocentesis are briefly described below. At RGI, we have been performing CVS and amniocentesis on a clinical basis for over 25 years. Our genetic counselors are available to discuss prenatal diagnosis options, if you have further questions or concerns.

Chorionic Villus Sampling (CVS)

CVS is typically performed between 10 and 12 weeks of pregnancy (first trimester). This can be beneficial to couples who wish to have prenatal test results earlier in the pregnancy. This allows for the option of a first trimester termination in the event of an abnormal result. CVS involves the withdrawal of placental tissue (chorionic villi) under continuous ultrasound monitoring either transcervically or transabdominally. The placental tissue or villi is derived from the same cells as the baby. Therefore, by testing the chromosomes in the villi, we are indirectly testing the baby's chromosomes. These cells are analyzed for chromosomal abnormalities, such as Down syndrome. Additionally, these cells can be sent to an outside diagnostic laboratory for mutation testing confirmation

RGI performs both direct and tissue culture analysis to assure greater accuracy and for the provision of preliminary results in 5 days. CVS does not provide information on neural tube defects. If a patient chooses to have a CVS, a Maternal Serum Alpha-Fetoprotein screen (blood test) and/or fetal ultrasound at 15 to 18 weeks is recommended to detect neural tube defects.

Amniocentesis

Amniocentesis is typically performed between 15 and 20 weeks of pregnancy. This procedure involves the removal of a small amount (one ounce) of amniotic fluid from the amniotic sac (where the fetus is located) under continuous ultrasound monitoring. Within the amniotic fluid are fetal skin and amniotic cells, which can be analyzed for chromosome abnormalities, such as Down syndrome. Additionally, these cells can be sent to a diagnostic laboratory for mutation testing confirmation. To identify the presence of neural tube defects, such as anencephaly and spina bifida, the level of alpha-fetoprotein (AFP) in the amniotic fluid is also measured. An elevated level of AFP may indicate the presence of a neural tube defect. If there is an elevated level of AFP, another test called an acetylcholinesterase (AChE) assay is performed. AChE in the amniotic fluid confirms the presence of an open neural defect. AChE detects 99% of open neural tube defects.

Fetal ultrasound is also recommended.

For chromosomal analysis, result-reporting times are typically within 5 days for CVS results and 7-10 days for amniocentesis results. The turnaround time for outside diagnostic testing may vary. Please speak with your genetic counselor for the specific details of your case.

MEDICAL TERMINOLOGY

Assisted Embryo Hatching – a procedure in which a hole is made in the zona pellucida of the early embryo. The embryo may more easily “hatch” out of the zona through the hole around the time of implantation.

Assisted Reproductive Technologies (ART) – a collective term which refers to a variety of medical procedures used to achieve pregnancy.

Aneuploidy – An abnormal number of chromosomes. An extra chromosome is called a Trisomy and a missing chromosome is called a Monosomy.

Blastocyst – the stage of development that the embryo is in when it enters the uterine cavity for implantation (typically 5-6 days after fertilization)

Blastomere – a single cell from the developing embryo

Chemical Pregnancy – A positive hCG level in the blood that fails to continue to rise and does not lead to a clinical pregnancy.

Clinical Pregnancy – When a positive hCG level is obtained and a fetal sac is seen in the uterus during an ultrasound.

Controlled Ovarian Hyperstimulation (COH) – The use of medications to stimulate growth and development of multiple ovarian follicles.

Crossing Over – The exchange of genetic material between the maternal and paternal copies of a chromosome/gene.

Cryopreservation – Freezing and storage of excess embryos from an ART procedure in liquid nitrogen tanks. May be thawed and transferred at a later date.

Embryo Transfer – A procedure during which embryos are placed into the uterus. This can occur on day 3 (around the 4-8 cell stage) or day 5 (blastocyst).

Estradiol (E2) – A steroid hormone produced by the growing ovarian follicle that is measured to assess the response of the ovaries to stimulatory medications.

Follicle – A structure in the ovary that has nurtured the ripening egg and from which the egg is released or retrieved.

Follicle Stimulating Hormone (FSH) – A hormone produced by the pituitary gland that stimulates the ovary to ripen a follicle for ovulation.

Follistim - Acts directly on the ovary to stimulate development of follicles (eggs)

Intracytoplasmic Sperm Injection (ICSI) – An assisted fertilization technique in which a sperm is microinjected directly into the egg cytoplasm.

In Vitro Fertilization (IVF) – A procedure during which an egg is removed from a ripe follicle and fertilized by a sperm outside the human body.

Inversion – A chromosome rearrangement in which a segment of a chromosome is reversed end to end. There are two types of inversions paracentric and pericentric.

Genetic counselor – a medical professional with specialized training in clinical genetics

Gonadotropin Releasing Hormone (GnRH) – A hormone produced by the hypothalamus that stimulates release of FSH and LH from the pituitary gland.

GONAL-F - Acts directly on the ovary to stimulate development of follicles (eggs)

Human Chorionic Gonadotropin (hCG) – A hormone secreted by the trophoblast that prolongs the life of the corpus luteum beyond its usual fourteen-day life span, resulting in the production of sufficient progesterone to support a pregnancy. It may be injected following controlled ovarian hyperstimulation to trigger ovulation and ensure adequate corpus luteum function. This hormone is the basis of most pregnancy tests.

Lupron – Synthetic gonadotropin releasing hormone analog administered to suppress secretion of LH and FSH to prevent premature ovulation.

Luteinizing Hormone - A hormone produced by the pituitary gland that triggers ovulation.

Meiosis – This term describes cell division that occurs during the formation of the mature egg and sperm. During meiosis, the number of chromosomes (genes) is reduced so that the egg and sperm contribute only half of the parent's genes to the embryo.

Nondisjunction – The failure of a chromosome pair to separate correctly during meiosis (cell division).

Nucleotide – Is a single DNA unit. There are four types of nucleotides that make up the genomic sequence: Adenine (A), Guanine (G), Cytosine (C), and Thymine (T).

Ovulation – The release of an egg from the ovary

Pergonal – Acts directly on the ovary to stimulate development of follicles.

Polar body – A polar body is a small cell that is naturally released by the egg or oocyte during the process of meiosis. The first polar body is released by the oocyte at the time of ovulation. The second polar body is released by the oocyte, at the time of fertilization. The polar bodies do not contribute to the developing embryo, but are naturally discarded by the oocyte during the process of meiosis.

Primer – A DNA primer is a synthetic segment of DNA that acts as a “starting point” upon which an enzyme can add nucleotides to replicate a specific strand of DNA.

Progesterone – Given to raise progesterone levels to promote preparation of the endometrium for implantation of an embryo.

Repronex – Acts directly on the ovary to stimulate development of follicles.

Translocation – A chromosomal rearrangement in which chromosome segments are exchanged between chromosomes.

FREQUENTLY ASKED QUESTIONS

Q: What is my first step?

A: Contact one of our genetic counselors to get information regarding the process, cost and to setup a free consultation. You can reach us by phone (773) 472-4900 or by email at rgiworld@gmail.com.

Q: How long between the time I send in my samples and the time I'm actually having the eggs retrieved?

A: This is determined on a case-by-case basis, but a general rule-of-thumb is no sooner than three months.

Q: How many embryos do they put back?

A: Most doctors will not transfer more than two embryos. This is decided by the couple and the physician based on how many embryos are unaffected, their quality, and personal issues.

Q: How many eggs are typically retrieved?

A: This depends upon a number of variables—the younger the woman, the more eggs she is likely to produce. There's no way to predict how many eggs will be retrieved, but we like to see at least 6 good follicles or we're likely to cancel the cycle.

Q: What happens if my cycle gets cancelled?

A: The physician will prescribe a different protocol than the previous one. This can be different medications, different dosages, place a woman on birth control pills, etc. It will be different for each couple. If your cycle is cancelled, we will refund the money paid for PGD (if you so desire) or can keep it for the next cycle. Depending upon when the cycle is cancelled, a portion of the monies may be kept to cover our costs.

Q: Do I have to travel?

A: For couples who would like both the IVF and PGD to be performed all in one place, it is necessary for you to travel to Chicago for the egg retrieval, testing and transfer. For those couples who would like to do IVF elsewhere and PGD with us, they will NOT need to travel to Chicago for any portion of the process.

Q: How long has RGI been doing PGD?

A: RGI has been performing PGD since it became available in 1990. We pioneered the polar body removal technology and are one of the most active centers offering PGD in the world. Our lab technicians are well trained in all techniques involved.

Q: What is the pregnancy rate?

A: There is no difference in pregnancy rates for couples going through IVF and PGD versus couples going through just IVF. This is very age dependent, but as a general rule, it is ~30-40% per IVF cycle.

- Q:** Can you perform Single Gene testing on blastocysts?
- A:** Yes, blastocyst (trophectoderm) biopsy can be performed on blastocysts and genetic testing can be done. If you are interested in doing a fresh transfer, due to timing restraints, it is recommended that the biopsy, testing and transfer all be done at RGI, but it may be possible to do it in conjunction with a cycle through an outside IVF center as well. Some centers opt to freeze after blastocyst biopsy testing and then do an FET cycle at a later date.
- Q:** Will my insurance cover this procedure?
- A:** In some instances, insurance companies have been found to cover the PGD testing and/or biopsy procedures. Some insurance companies will cover the IVF procedures (although usually this requires a diagnosis of infertility). You should contact your insurance directly to see if they will cover any or all of the procedures.
- Q:** Is there a waiting list?
- A:** No, there is no waiting list. Please contact a genetic counselor directly to get the process started.
- Q:** What if I'm on the birth control pill now, should I stop this?
- A:** It depends upon the type of birth control pill. It will be important to check with your IVF physician before making any changes to your pill.
- Q:** Can you test for multiple Single Gene conditions on one cell?
- A:** It may be possible to do multiple diseases on one cell at an additional cost to you. Remember, though, we have a small amount of DNA and a very limited timeframe, so we usually can test only for one or two things. Feel free to discuss this with us. In general, we are testing for one specific genetic condition. PGD does NOT test for all genetic conditions. PGD also does NOT test for birth defects or mental retardation.
- Q:** What is the risk for multiple births (e.g., twins or triplets)?
- A:** This will depend upon the number of embryos transferred and the quality of the embryos transferred. Most centers see a ~5-10% rate of multiple gestation
- Q:** Where can I find more reading material regarding PGD?
- A:** Your genetic counselor can provide you with a list of relevant publications.