The purpose of the genetics consult

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I have been working with Zouves Fertility Center since January 2003, providing genetic counseling for all couples and ovum donors in their program. People undergoing IVF generally do not receive genetic counseling prior to their cycle. As a result, the opportunity for applicable genetic testing/counseling in the *preconception* period is often lost. Family history risk assessment in an infertility setting allows couples to learn about their genetic risks prior to pregnancy. For some couples it provides information about the causes of their infertility. Armed with this knowledge, couples at risk of transmitting genetic conditions may choose to take full advantage of technology such as PGD. The number of couples with a history suggestive of an increased risk for mental retardation or birth defects in their offspring is relatively low, but screening all couples is necessary to identify these individuals. For people without an identified risk for mental retardation or birth defects, most have other diseases in the family which have a genetic component.

Ovum donors are usually screened through the use of a family history questionnaire, usually focusing only on first degree relatives and grandparents. The majority of questionnaires that I have seen omit nieces, nephews, aunts, uncles and cousins. Most gamete donor programs do not utilize genetic counseling services for family history risk assessment and do not obtain a three generation pedigree. If a donor has a positive genetic test result, many donor agencies do not refer for genetic counseling and do not adequately address the implications for the donor and her family.

I reviewed the charts of patients and ovum donors from January, 2003 - May 2004. Of 455 couples, 296 (65%) had an identified increased risk. Of 111 donors, 26 (23%) had an increased risk.

The importance of family history risk assessment

Genetic risk assessment is not only valuable for people who have identified inherited diseases in their family. Advances in genetics, especially in the past two decades, have increased the utility of the family history as a screening tool in all clinical settings.

Your family history contains critical information about your health, including risks for certain genetic conditions and health problems, such as heart disease, diabetes and some cancers. By knowing your family health history, you can learn what health concerns you may be at risk for in the future, and what options are available, such as early detection or prevention.

Historically, genetics has called to mind rare, single gene disorders or chromosomal abnormalities that concern a relatively small number of families. In the wake of the Human Genome Project, this is no longer the case. Every disease has some genetic component, with the exception of conditions resulting from accidental trauma, but medical practitioners and our health care system as a whole are unprepared for the rapid advances in genetics and their implications for practice. This is becoming increasingly apparent as patients respond to increased coverage of genetics by approaching their providers with questions, concerns, information, and often misinformation culled from the media or the internet. Ideally, every practitioner should be incorporating genetic thinking and genetic principles in the provision of care.

The reality is that most physicians do not take a detailed family history, which can play a critical role in diagnosis and lay the foundation for accurate risk assessment. Even when a clear Mendelian pattern of inheritance is not evident, a detailed family history may lead to the conclusion that certain individuals are at increased risk for conditions warranting closer clinical observation, and when possible, educational and preventive measures. The synthesis of medical information, combined with the graphic representation of inheritance through multiple generations (the pedigree or family tree), frequently leads to medical insights that otherwise might have been overlooked.

The family history is also an evolving record. It expands and matures through time as patients and families move through developmental life stages. By recording births and deaths, marriages, reproductive outcomes, and medical characteristics, the family history becomes an invaluable resource.

Health professionals have little time to collect extensive family history information, but I encourage you to take a copy of your medical pedigree to appointments (this is provided as part of the consult). The hope is that raising awareness of significant health risks revealed in the family history will lead to healthy lifestyle changes or improved medical screening.

Why is ethnicity important?

In almost every population or ethnic group, certain genetic conditions occur more frequently than in the general population. Once a genetic mutation occurs in an individual or population, it is conserved from generation to generation over many years as people mate and marry with partners from the same geographic region or racial background as themselves.

Specific conditions occur more commonly in different ethnic groups. All are inherited in an autosomal recessive fashion, meaning that both parents have to be carriers for the same condition in order to have an affected child. While the carrier rate is highest in the below mentioned groups, a person of any ethnic group can be a carrier for any disease. The only way to know if you are a carrier for a recessive disorder is to have carrier screening. At ZFC, carrier screening is offered by ethnic group to patients as part of their pre-screening lab work.

Condition	**Birth rate**	**High risk group**
Cystic fibrosis	1 in 25	Caucasian
Sickle cell anemia	1 in 10	Black
Tay-Sachs disease	1 in 30	Ashkenazi Jewish
Canavan disease	1 in 40	Ashkenazi Jewish
Familial Dysautonomia	1 in 27	Ashkenazi Jewish
Gaucher disease	1 in 10	Ashkenazi Jewish
Beta-thalassemia	1 in 25	Greek/Italian
Alpha-thalassemia	1 in 22	Asian

Preimplantation genetic diagnosis

Preimplantation genetic diagnosis (PGD) allows genetic analysis to be performed on early embryos prior to implantation and pregnancy.

Couples who elect to have PGD undergo an in vitro fertilization (*IVF*) or *ICSI* cycle and embryos are formed as usual in the laboratory. Embryos are then biopsied with very fine glass needles and tools under microscopic observation and control to obtain one or two sample cells (blastomeres) for genetic analysis. Embryos whose biopsy results are normal are then available for immediate transfer into the uterus, with additional embryos (if available) frozen for subsequent transfer. Animal experiments and a very large experience with PGD in humans have documented the safety and efficacy of this technology for preventing genetic disorders and producing the births of normal children.

Preimplantation genetic diagnosis is being increasingly used at state-of-the-art IVF centers. Screening of early embryos for common chromosomal aneuploidies like Down syndrome (trisomy 21) may be helpful in many couples undergoing IVF, especially those with a history of recurrent pregnancy loss, repeated IVF failure or advanced maternal age. Not only has it been established that this technology can improve implantation and ongoing pregnancy rates in some couples by permitting enhanced selection of more normal embryos for transfer, but the rate of detectable trisomies like Down syndrome in offspring should theoretically be reduced by these methods. PGD can also be used in prevention of X linked genetic diseases by implanting only female embryos. For couples in which one partner carries a chromosomal translocation may experience recurrent miscarriages or the birth of a child with multiple birth defects. PGD may be used to select normal embryos to transfer in order to prevent such outcomes. PGD can also be used for a variety of inherited single disorders, to select out embryos that carry the specific gene mutation.

Genetic factors involved in infertility

Male factor infertility

There are several male factor infertility diagnoses associated with genetic risks. Nonobstructive azoospermia is associated with a 15% risk for a chromosome abnormality, with Klinefelter syndrome being the most common (an extra X chromosome in a male). There is a 13% risk for a Y chromosome microdeletion and some risk for a chromosome translocation or inversion. Oligospermia carries about a 2% risk for a chromosome anomaly, especially translocations, and a 6-8% risk for a Y chromosome microdeletion. A sperm count of less than 5 million carries a 10% risk. Paternal chromosome anomalies increase the risk for miscarriage, birth defects, developmental delay and infertility.

Bilateral congenital absence of the vas deferens (CAVD) is associated with up to an 80% risk for at least one mutation in the cystic fibrosis (CF) gene. For unilateral CAVD, there is up to a 40% risk for a CF mutation. There is also an increased likelihood of having the 5T variant in the CF gene for people with unilateral or bilateral CAVD.

Certain single gene conditions are associated with male factor infertility such as Noonan syndrome, myotonic dystrophy, adult polycystic kidney disease, partial androgen insensitivity, Kartagener syndrome, and Kallman syndrome.

Female factor infertilitly

Some female factor infertility diagnoses are associated with genetic risks. POF has been associated with a 3%-13% risk for fragile X carrier status. Structural or numerical X chromosome anomalies are another cause and other single gene factors (such as hormone receptor genes) are under investigation.

Genetic risk associated with IVF

As with many medical advances, there are benefits and risks associated with the currently available high technology solutions to infertility, such as In Vitro Fertilization (IVF) with Intracytoplasmic Sperm Injection (ICSI). Such technology has allowed men who would otherwise have no chance for paternity the opportunity for biological fatherhood. At present, approximately 60% of IVF cases are performed with ICSI, and the majority of those are performed for male factor infertility. This highly technical approach currently has two genetic risks associated with it:

1) the increased chance of children conceived using ICSI to have an extra or missing sex chromosome as compared to children conceived without ICSI (8/1000 compared to 2/1000, respectively). Depending on the woman's age, maternal age risk alone may be higher than the ICSI risk.

2) the risk of passing on to offspring the genetic factors that contributed to the male factor infertility, such as chromosome abnormalities, Y chromosome microdeletions, or cystic fibrosis.

3) The use of IVF alone (without ICSI) has been the subject of study regarding a possible of increased rate of methylation disorders, such as Beckwith-Wiedemann (BWS) and Angelman syndrome. The best study estimates a 7 fold risk for BWS in the IVF population, which is still less than a 1% risk.