

**Establishing the Demographics and Rationale for
Use of Preimplantation Genetic Diagnosis and Screening
in Arizona and Outlying Locations**

Thesis submitted to the
University of Arizona College of Medicine - Phoenix
in partial fulfillment of the requirements for the degree of
Doctor of Medicine

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Class of 2012

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DEDICATION

To Dustin
To my family

ACKNOWLEDGEMENTS

Many thanks to my mentors, Katherine Hunt MS, CGC and Jason Robert PhD, for their tireless work, great ideas and guidance

Special thanks to Dr. Diana Petitti for her kind support, assistance with the project

And to Dr. Jacqueline Chadwick who inspired me with the idea in the first place

PROJECT ABSTRACT

Background:

Pre-implantation genetic diagnosis (PGD) and pre-implantation genetic screening (PGS) test for genetic diseases prior to implantation in cases utilizing in-vitro fertilization. While PGD/PGS use is expanding, ramifications for patients and society are unclear.

Study Question: What is the current utilization and patient demographics of Preimplantation Genetic Diagnosis (PGD) and Preimplantation Genetic Screening (PGS) in Arizona Infertility clinics?

Significance: Though PGD/PGS usage has grown, gaps remain in the understanding of current U.S. clinic experience. This study addresses these, focusing on the diverse Arizona patient population, by surveying all Arizona in-vitro fertilization clinics.

Methods: Using capture-recapture method, all IVF-providing clinics within Arizona (n=11) were identified and sent an anonymous survey. Surveys were then analyzed.

Results: Nine of eleven clinics responded. While patient demographics were similar, patient numbers per clinic differed and were not correlated with length of operation. Genetic tests differed amongst

clinics. Most favored self-regulatory models, recognized the Internet as the primary source of patient education, and valued increased PGD/PGS education.

Conclusion:

Patient demographics revealed that minority populations were not proportionally represented when compared to census data. Clinics offered differing sets of genetic tests and criteria for seeking these tests, indicating varying opinions amongst clinics about the ethicality of PGD/PGS.

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Introduction

Background

In the past three decades, with the development of techniques for assisting human reproduction, culminating in the first “test tube baby” in 1978, the growth in numbers and technique has led to another new era in 1990, that of preimplantation genetic diagnosis (PGD) (Verlinsky 1990). With PGD came the ability to diagnose prior to implantation and traditional prenatal diagnosis could, allowing identification of the genetic predisposition of potential fetuses prior to insertion into the uterus using the In-Vitro Fertilization (IVF) technique. IVF is the method by which human eggs are fertilized with human sperm outside of the human body and the embryo is then introduced into a uterus to complete a pregnancy. PGD currently continues its ever-increasing expansion, ensuring the health of the embryo even prior to conception (Simpson 2010), assisting those patients who would avoid pregnancy termination once the embryo is transferred and implanted, and even touching the area of HLA-typing for sibling compatibility donor matching and preimplantation sex-selection for family balancing (Verlinsky 2003). With this there is a still primary focus in providing a preimplantation screen for Mendelian

disorders from chromosomal aneuploidy and translocation, single gene disorders, to now even later-life disorders of which cancer predisposition and Alzheimer's disease are principal, and more multifactorial and non-Mendelian disorders. For patients at less genetic risk, there is also now PGS, Preimplantation Genetic Screening, primarily used to screen for aneuploidy in advanced maternal age patients, and others with some risk but nothing identified by history.

For purposes of this paper, the 2008 American Society for Reproductive Medicine (ASRM) definitions will be utilized. Preimplantation genetic diagnosis (PGD) “applies when one or both genetic parents carry a gene mutation or balanced chromosomal rearrangement and testing is performed to determine whether that specific mutation or an unbalanced chromosomal complement has been transmitted to oocyte or embryo.” Preimplantation Genetic Screening (PGS) “applies when the genetic parents are known or presumed to be chromosomally normal and their embryos are screened for aneuploidy” (ASRM 2008).

As the diagnostic method has burgeoned among IVF providers in the US, Europe, Australia, and has been improved upon, testing

blastomeres, polar bodies, blastocysts and utilizing FISH and PCR techniques, debates surrounding the procedure have increased. The number of successful births went from approximately 1000 in 2004 (Verlinsky, et al. 2004) to now more than 10,000 successful births (Simpson, 2010), quickly increasing in rate. What this means is that PGD potentially doubles the success of IVF cycles and pregnancy rates in some studies, and that many parents who are at a higher genetic risk for transfer of familial disorders or aneuploidy with advanced maternal age, greatly increase their odds of successfully carrying a pregnancy to delivery.

With this astounding possibility come debate, questions and much concern over what utilizing preimplantation genetic testing might mean both to the parents, the subsequent fetus, and the larger implications on the patients' families and society as a whole. Concerns for the long-term health of the selected embryo after pregnancy have been raised, and has yet to be fully ascertained as the earliest neonates born using this technique are just completing their second decade of life. Beyond concerns for physical ramifications are psychological and ethical fears (Iwarsson 2011, Karatas 2010). The question of PGD leading to a eugenic-like emphasis on selecting and implanting only

those embryos with certain desired qualities—non-disease related. The concern of the ‘designer’ baby exists, even as others point to the necessity of selection with IVF regardless of PGD (Lavery 2004). It is argued that PGD allows for selection that would decrease the likelihood of spontaneous abortion in mothers who are already at high risk of failed pregnancy, and that it also works to decrease the number of elective abortions during a subsequent pregnancy, which might occur for genetic disease related concerns (Iwarsson 2011). It would be catching the disorder prior to implantation, thereby saving money and much patient anxiety. Confounding this are some of the newer practices, that of family balancing via non-disease related sex-selection, and the potential for HLA-matching future siblings with older siblings, to provide a pregnancy and thus, cord blood to the living older brother or sister who is sick and is need of a donor with analogous HLA for blood transfusion or bone marrow transplant (Knoppers 2006, Lavery 2004).

Currently, the heated conversations continue with advocates on both sides. All the while, IVF clinics across the nation grow and provide assisted reproductive care to an increasing patient base. The number of infants born with reproductive assistance and IVF is 1% of

all infants born. Further, the number of IVF cycles utilizing PGD most likely exceeds 50,000 newborns worldwide (Simpson, 2010), with more than 74% of IVF clinics offering PGD services (Baruch 2008). And the debate over the place of regulation continues. Various European nations have led the way in PGD clinic oversight, countries such as England with its well-developed HFEA (Human Fertilisation and Embryology Authority) and the Netherlands under the Special Medical Treatments Act (Aarden, 2009). The United States, has maintained less monitoring, although the CDC requires annual reports on cycle numbers, success, techniques and screening types from all clinics in the United States that are offering preimplantation genetic testing—screening and full diagnosis, and the American Society for Reproductive Medicine (ASRM) promulgates some practice guidelines (Cooper 2010).

Significance

In 2008, a national survey of IVF clinics was done, focusing on practices and procedures but not patient populations by state or clinic. Currently, there is no data on the extent of use and how it relates to changes in usage, demographics, or financial considerations

of clinical implementation of PGD in the state of Arizona. For that matter, nor has this intersection of concerns been studied nationally. A study, done in 2007, surveyed clinicians in UK, Italy and Sweden with a qualitative, oral series of questions of their thoughts on implementation of PGD, benefits and what the providers believed the benefit of PGD and PGS to be (Zeiler 2007). However, to date, a survey seeking to understand clinics' overall assessment of their own practices utilizing PGD, qualitative information potentially, but reported as quantitatively for comparison as is possible—such a survey has not been undertaken. Since the state of Arizona has a well-defined, exhaustive set of IVF clinics offering PGS and PGD, located in two major cities, Phoenix and Tucson, the study pool –11 clinics in total—is circumscribed, yet large enough for a detailed study using their reported data of PGD as it is used in Arizona.

Furthermore, the study's goal is to provide insight into PGD utilization in Arizona and surrounding areas and also of the many minority population groups well represented in the state. Because Arizona comprises American Indian population of 4.7% --compared to the 1.0% national average (US Census Bureau, 2010) and a Hispanic population of 29.6%--compared to the national average of 15.1%, (US

Census Bureau, 2010) the findings of this proposed survey will delineate the extent to which PGD is utilized by these typically underserved groups.

Question and Aims

The goal of this study is five-fold. First, it is to combine and assess Arizona PGD populations, giving a snapshot beyond maternal age to cultural demographics and what genetic tests they are asking for.

Second, to assess changes in growth and promotion of PGD by IVF clinics, from the clinic opening till currently, and to step back and look at how in light of some of the originally-cited reasons for implementing PGD how those reasons for using PGD may have changed in the IVF clinic practice.

Third, to solidify an understanding of how the economic situation affects this specific patient population and its access to the PGD service, as well as to begin conversation regarding how this might or should change as PGS and PGD technology improves and costs potentially change.

Fourth, to provide understanding from this survey, highlighting for obstetrician-gynecologists and infertility specialists the use of preimplantation genetic testing and the extent to which those populations are educated and then referred for PGD.

Fifth, to ascertain what the clinics' view on the politically charged issues of oversight for PGD by external/governmental bodies and if increased emphasis on PGD within the healthcare community and greater education of the public would benefit more patients or be more likely to overwhelm the current IVF healthcare systems. During the course of this study, this last issue of public applicability was demonstrated in the increased emphasis by the Arizona State Legislature ruling against abortion for purposes of sex-selection, which could pose difficulty by implication for sex selection for family balancing purposes as undertaken using PGD (HB 2443, Arizona State Legislature).

The specific aim and implicit question of the survey study is: What is the current utilization of Preimplantation Genetic Diagnosis (PGD) and Preimplantation Genetic Screening (PGS) in Arizona Infertility Clinics, including the demographics of the patient population and their reasons for pursuing PGD and PGS

Materials and Methods

Subjects:

The population surveyed was the complete sample of all IVF clinics in the state of Arizona, specifically those providing preimplantation genetic diagnosis and screening procedures. To identify the entire number of these IVF clinics, the capture-recapture method was utilized, using multiple and different sources to compare and identify all Arizona clinics falling within this grouping. Specifically many of these sources were national bodies of reproductive technologies: American Society for Reproductive Medicine, Society for Assisted Reproductive Technology, Society for Reproductive Endocrinology and Infertility, and confirmation from the reports of the website of the CDC providing most current clinic data as they self-reported. In this way, a list of the purported clinics in Arizona was assembled and then the entirety of that group confirmed.

Oversight:

While the subjects were the clinics, yet to ensure adequate oversight and warrant for the study and protection of the subjects, the

study sought and was granted Exempt Approval by the University of Arizona Internal Review Board Human Subjects Protection Panel.

Contacting the clinics:

Each clinic so identified was then contacted by telephone, to ascertain willingness and availability to participate in the survey and to notify them of the arrival of the survey by mail. Their informed consent was obtained as part of the survey mailing. Two copies of the survey were sent out by mail to each clinic, the first mailing after phone introduction and the second later on, as a reminder to all clinics. Accompanying each mailing of the survey tool was a cover letter with research introduction, explanation of the survey process, and notification of their rights as subjects. Consent to participate was implicit in their reply with a completed, anonymous survey.

Anonymity was preserved by written and oral instruction to each clinic to return their survey without any identification added to either the survey tool itself or the envelope. The surveys were to retain no specific clinic identification, to provide no means to relate answers to any one clinic.

Additionally, each clinic was requested, in order to quantify answers and preserve some uniformity in the survey responses, that either a lab manager or director, or one of the primary medical providers, or medical director be the primary respondent to the survey, answering on behalf of the clinic. The goal was to obtain a picture of each clinic's experience using PGS, PGD.

Survey tools:

Using early PGD literature, a list of pertinent clinical questions was outlined, attempting to provide semi-quantitative means of evaluating individual experiences and the demographics of Arizona IVF clinics providing PGS, PGD. The survey was designed in a way to report results in a numerical representation when possible, while including individual responses when they used free text to report. The survey comprises question categories regarding

1. General Clinic Information,
2. Basic demographic information of the PGD, PGS clinic patients
3. Patient financial data
4. Each clinic's insight and suggestions regarding change to current reimbursement

5. Each clinic's experience using PGD
6. Each clinic's position on information sharing, referrals for new patients.
7. Recommendations and opinions on governmental oversight and monitoring.

Analysis

After consultation with a biomedical statistician, the approximate size of the subject pool was estimated and the best method of identifying all clinics providing PGD was determined to be by Capture-Recapture method. (This was assuming a somewhat smaller subject pool ($n > 50$) within the state, as per expert opinion.) Based on that assumption, when the number of clinics was found, and the completed surveys were returned, the biostatistician ascertained that the analysis for the constricted group would best consist of simple numerical comparisons. The biostatistician also determined that calculating the p value would be of no assistance, because of the value of n would render any p value significance useless. Therefore numerical data when available were compared and the mean, mode, median, and other mathematical representations were utilized for

significance and comparability. After the data was categorized for comparing, it was analyzed for significance and the results will be reported in tabulated form primarily for comparing clinics. In addition, when actual data was provided from all clinics, the sum total was calculated to provide a sense of Arizona's overall patient statistics.

Results

The survey response

As a result of the capture recapture method used in identifying all IVF clinics currently in operation in the state of Arizona, eleven clinics were identified. All eleven clinics were then contacted and surveys mailed to each one. Ten clinics completed the survey representing a response rate of 91%. However, in comparing the responses from all ten surveys, the reports from two surveys were almost identical. Thus, the overall clearly unique clinic response rate to the PGD/PGS survey was 82% (nine clinics responding out of eleven possible).

General Clinic Information data

The clinics responding represented a wide range of lengths of time in operation, as noted below in Table 1. The mode was the year 1995, and the opening dates ranged from 1980 to 2010 as the newest clinic responding.

Decade approximate	1980-1989	1990-1999	2000-2010
# clinics opened	1	5	3
Total # of patients seen by clinics opened in each decade	5	108 (1108*)	16

Table 1. Notes the distribution by approximate decade of participant clinics and when they opened, however the 2000-decade includes clinics opened during eleven years, including 2000 and 2010.

* If the clinic reporting 1000 patients treated is included

# PGD PTS SEEN AT CLINIC	2	3	5	10	12	14	75	1000
# of clinic s	1	2	1	1	1	1	1	1
Median				Mean incl. 1000		Not including 1000		
10				125		16		

Table 2. Demonstrates extent of clinic utilization of preimplantation genetic diagnosis and screening as self-reported. Average number of Arizona patients using PGD is presented including the 1000 patients seen reported and as well as not including that clinic's response.

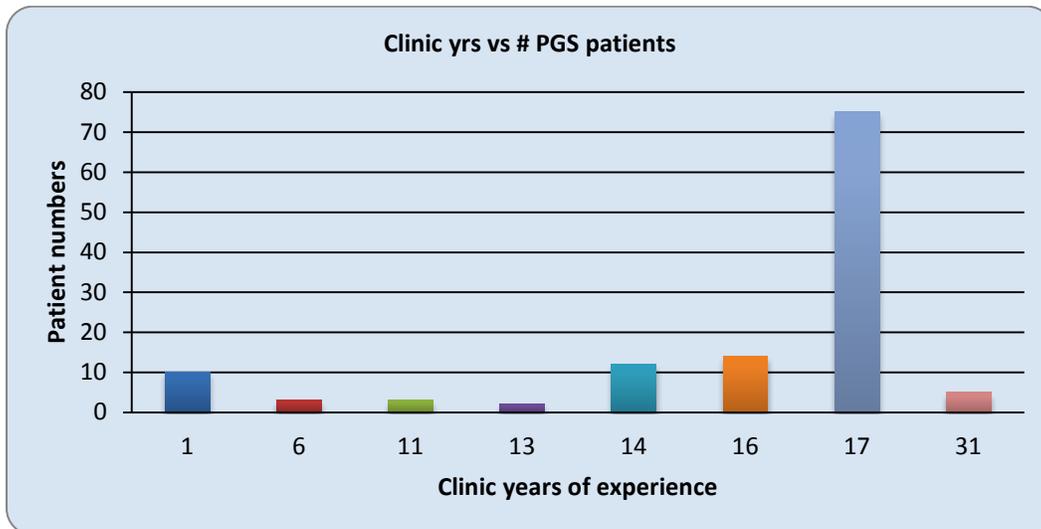


Figure 1. Comparison of years of clinic experience with # of PGS patients. X axis represents number of self-reported clinic years of experience. Y axis represents # of PGS patients seen. Clinic reporting 1000 PGS patient cases excluded in this, for illustration.

Types of genetic tests utilized

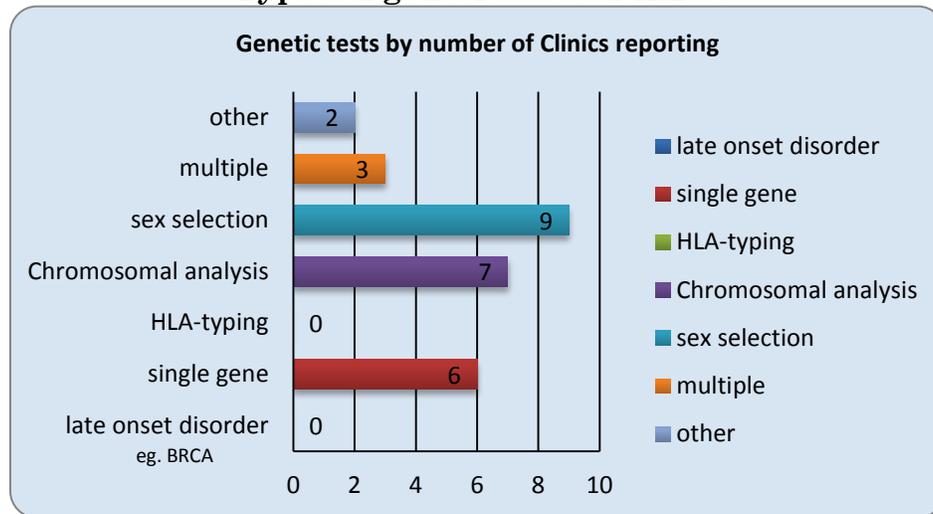


Figure 2. Clinic by numbers, self-reporting the variety of genetic tests they had performed for their patient population. Late-onset disorders indicated disorders that do not present until later age in the patient. As may be seen, no clinics reported genetic testing for any.

Clinics also reported on their overall number of experiences using PGD or PGS within their IVF patient population, as Table 1 and Table 2 illustrate. This value varied significantly, depending on the clinic, yet not necessarily correlating with number of years since clinic opening, although the most similar group of respondents were those who had opened their clinics in the 1990s.

Figure 1 is used to demonstrate any relationships between length of clinic's practice in Arizona providing IVF services and the number of patients seen for PGD/PGS treatments during this time period. As can be seen, the clear outlier was the clinic reporting 1000 patients using preimplantation genetic testing.

With clinic reporting 1000 patients excluded, the other clinics with the variance in their patient numbers could better be appreciated graphically. This is why there is a mixture of figure reporting that clinic's statistics, with some selecting that data out, so as not to alter the overall clinic reports. If that clinic's data is treated differently, it is indicated in the graph.

When questioned about which preimplantation genetic tests were used, the majority of the clinics reported sex selection (non-medical vs. medical reasons were not specified in this question), as

Figure 2 illustrates. The majority of clinics also commonly employed chromosomal testing. Specific tests mentioned by individual clinics were: Cleidocranial dysplasia, aneuploidy, family balancing translocation analysis, Cystic Fibrosis, Huntington Disease, p53 variant (the clinic reporting did not specify further), to name some.

HLA-typing was commented on by one clinic that it had some patient interest in it, but no clinics reported actually performing genetic analysis for the purpose of HLA sibling typing (see Figure 2).

Age groups	% pts in Arizona
18-25 yr old	2.6%
25-30 yr old	2.8%
30-35 yr old	14.5%
35-38 yr old	22.6%
38-40 yr old	20.4%
40+ yr old	36.8%

Table 3. Taking the numbers reported by clinics, this approximate table demonstrates the overall patient statistics, with a few patients not distinguished by percent values by a clinic (n=3).

PGS/PGD patient ages

Total number of Arizona PGD/PGS patients, as calculated from # in each maternal age group, including the 1000-patient reporting clinic = 1148.

Additionally, there was no mode age group, representing the largest patient group reported by a majority of the clinics, because several age groups tied for highest placement: Ranges (30-35), (35-38), (38-40), and (40+.) Overall, the largest percentage of patients did fit into the 40+ age range, however. This data does include the 1000 patient number report.

Finally, one clinic did not respond with details of its patient age span, but its total reported PGS patient numbers were 3. However, their data was not able to contribute to the values and comparisons seen above.

Patient demographics by race:

The racial demographics were determined by overall patient census reported by each clinic superimposed with approximate percentages of patients by racial group. Correlating the two enabled the approximate power of each clinic's reporting to be obtained. Since

there were some non-responders, the results are only reported in relation to each clinic. In answer to this survey question, there were 2 non-responding clinics. The top 3 reported patient populations by race, selected by top 3 modes:

White Non-Hispanic

White Hispanic

Asian American

The above groups were determined based only on those clinics reporting their patients' racial backgrounds, a sub-pool of the total clinic group. For this reason, the data reported here is not defined by numerical values.

Demographics by religious preference:

Three clinics were virtually non-responders. One clinic reported only the lack of any Catholic patients utilizing PGD or PGS, another only the lack of Native American religious belief. Another clinic reported that none of its patients had a religious preference, of those listed in the survey. A fourth clinic reported patients of the Hindu and other categories, again, another reported only under 'other' and identified Orthodox Jew as the group. Finally, one clinic reported

patients of Catholic, Evangelical Protestant, Mormon, Muslim, Atheist,
and other categories.

Clinics with patient insurance coverage for PGD		Clinic with 5%: coverage not disease related
Yes	2 clinics-10% and 5% of their pts respectively	Clinic with 10%: late-onset, genetic predisposition and single gene disorders
No	9 clinics reported no	
Unknown	1 clinic	

Table 4. Most clinics had not experienced insurance coverage for their patient populations.

Financial expense and patient coverage:

In response to the question of what percent of total PGD patients are covered by Medicaid clinics were unanimous in stating that none of their patient supported by Medicaid while treated by the clinic.

Regarding the question of insurance coverage, the replies were more varied, as Table 4 demonstrates.

6 replies: none

1 reply: unknown

1 reply at 10% of their patients (clinic reporting 10 overall patients)

1 reply at 5% of patients (clinic reporting 75 overall patients)

When asked about the details of the testing covered by their insurance, these two clinics replied the one in regard to 5% of their patients, that coverage was not disease related. The clinic that reported 10% of their PGD patients reported that the disorders covered were late-onset, genetic predisposition and single gene disorders.

Further, no clinic was aware of any neonate born by PGS selection through the clinic who then was uninsurable after birth due to a disease diagnosis using genetic testing.

Financial expense of PGS and Clinic opinion on reimbursement

Each clinic was queried about the charge of PGS/PGD work up through their clinic, the responses ranged from \$2400 to \$21,000. The most frequently cited was \$5000 and \$6000; see Figure 3 following.

In response to if increasing financial and access and patient educational awareness truly be of benefit in providing PGD/PGS to patients who would benefit from it, but might currently be restricted in their access to it, the clinics were divided in response, 5 stating that lowering costs could increase access, while 4 stating that such measure would not, in fact, be helpful.

Among the respondents in the affirmative were both clinics that had reported a portion of their PGS patients receiving some insurance coverage for their PGS

Over whether insurance companies should cover the additional expenses of PGD procedures, there was again variability.

Five clinics replied no: insurance companies should not cover PGD expenses.

One clinic replied yes: insurance companies should cover PGD expenses

Three clinics replied that it depends—1. Based on the nature of the diagnosis. 2. Based on success rates and whether PGD can be shown to decrease the rates of multiples and to increase live birth rates, and 3. Based on the employer’s decision to purchase the insurance.

Interestingly, the clinic reporting 5% of patients with insurance coverage stated that insurance coverage should depend on the employer’s decision to purchase, and that the other clinic reporting insurance information stated that no, there should not be insurance coverage for PGD.

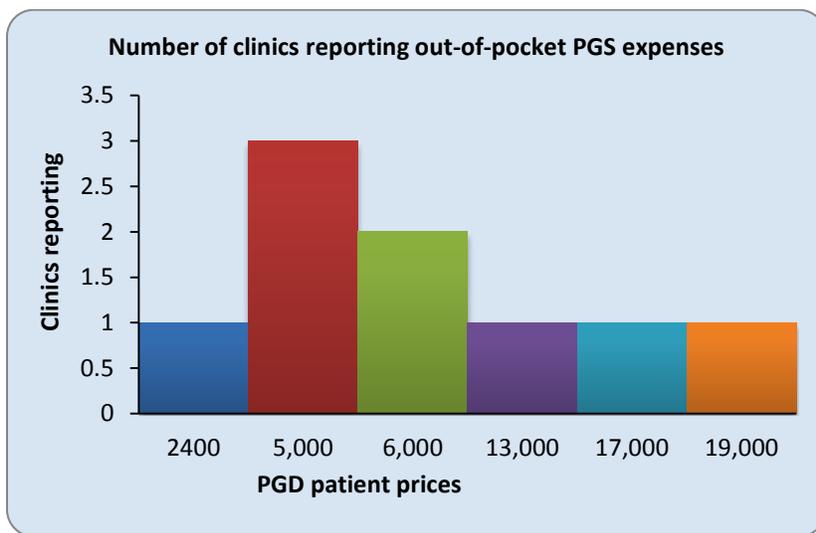


Figure 3. Number of clinics reporting in each expense category on Y axis, and overall expenses reported by each identified in X axis. This was asked as what was the price for the patient, covering just the PGS/PGD procedure, and the question was worded in that way specifically.

Clinic Experience providing PGS/PGD currently and previously

Clinics responded regarding their own experience in offering preimplantation genetic testing, commenting on course of demand and overall utilization of the testing within the scope of their clinic's practice. See Figure 4 below.

As Table 5 demonstrates, the clinics further commented on the effect of current economic change and difficulty and any associated effect on the patient demand for PGS in the face of national financial adjustments within the same time period.

Another question that has arisen during the years since PGD has become increasingly popular was that of a potential preference by ethical or religious IVF patients identifying with that description, but uniformly the clinics had not noticed a proportionate increase in religious patients desiring preimplantation genetic testing services.

Clinics were mixed in their assessment of whether their IVF patient base had used PGD or PGS to avoid termination later in the pregnancy.

Five clinics responded affirmatively, four more said that it did not affect their IVF patient decisions.

Clinics varied minimally as to whether patients requesting use of PGD in addition to their IVF were more likely to *expect* to deliver healthy children because of the additional use of the genetic testing prior to implantation. As Table 6 indicates, one clinic stated their patients did not have an increased expectation of delivering healthy children after utilizing preimplantation genetic testing.

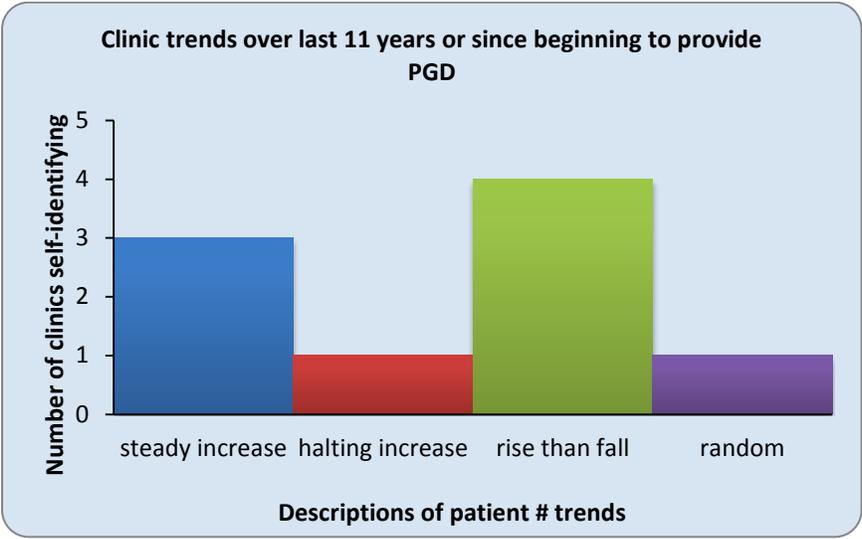


Figure 4. Y axis indicates number of clinics reporting each trend, X axis describes the various trends acknowledged by the clinics.

PGD patient volume descriptions of adjustment during economic changes	Number of clinics reporting adjustment
Remained approximately the same	5 clinics identified
Increased	1 clinic identified
Decreased	3 clinics identified

Table 5. Description of patient demand for PGS during recent economic changes

Patients expecting to deliver healthy babies with PGD?	Number of clinics responding
No	1 clinic responded
Yes	8 clinics responded

Table 6. Patients expectations of a healthy baby after utilizing PGS with their IVF procedure.

Interestingly, of the eight clinics stating there was that expectation when using PGD, five of the clinics had noted patients specifically using PGD as a measure to avoid an elective abortion later during the pregnancy. The other three clinics reported no such reason for using the testing among their patients.

In regard to HLA-type matching, only two clinics commented that they had patients who were either interested or requesting that particular application of PGD.

Of the patients for whom the clinics had successfully implemented PGS into their IVF care, those who returned varied significantly:

Range was from 0%-75%, with the majority (4 clinics) describing no returning patients. The median reported was 5% return rate (100% if they had cryopreserved embryos).

Sex-selection as a part of each clinic's protocol and PGD procedure also was addressed. Two clinics stated specific avoidance of providing sex selection as part of their procedure, but one indicated that no active withholding of that information.

The seven clinics which do not *avoid* providing or which do offer sex selection to their patients, in regard to social groups seeking sex

selection, most made no response (n=3), but of the clinics that did two clinics stated that the social groups represented varied. One other clinic stated no social group variance but did not elaborate, and the final clinic stated that their patient population seeking this specific test was primarily Asian Indian. This same clinic had also described their patient base as comprising 40% Asian Indian as well (the highest percentage reported by a clinic for cultural representation).

Of those seven clinics willing to provide sex selection as part of their procedure, four clinics denied any patient groups that specifically refused selection of the embryo's sex, the three additional clinics made no response.

When queried about the adequacy of discussion and the current level of national standardization in regard to the use of sex selection as a part of PGD procedure, clinics were not in agreement. Seven clinics asserted that current standardization was appropriate, while two clinics, interestingly, did not.

One of the two dissenting clinics was also one of the two clinics that avoid sex selection as part of the PGD procedure. The other clinic that said no was the one reporting the largest PGD patient numbers (n~1000).

Referrals, PGD education, and national regulation of preimplantation genetic testing

Information source, as described by the clinics about where the patients received their information about their clinic and preimplantation genetic testing, was highlighted. For illustration of their information sources, see Figure 5.

One clinic did not know the source of its PGD patients' information, however all other eight clinics did make a response as to some information source.

The clinics responding noted unanimously the presence of the Internet as an important initial resource in education concerning the genetic testing associated with IVF. Other important information sources included previous experience and literature, with Obstetrician/Gynecologists as initial source supplying a smaller pool of patients with their initial education about PGD.

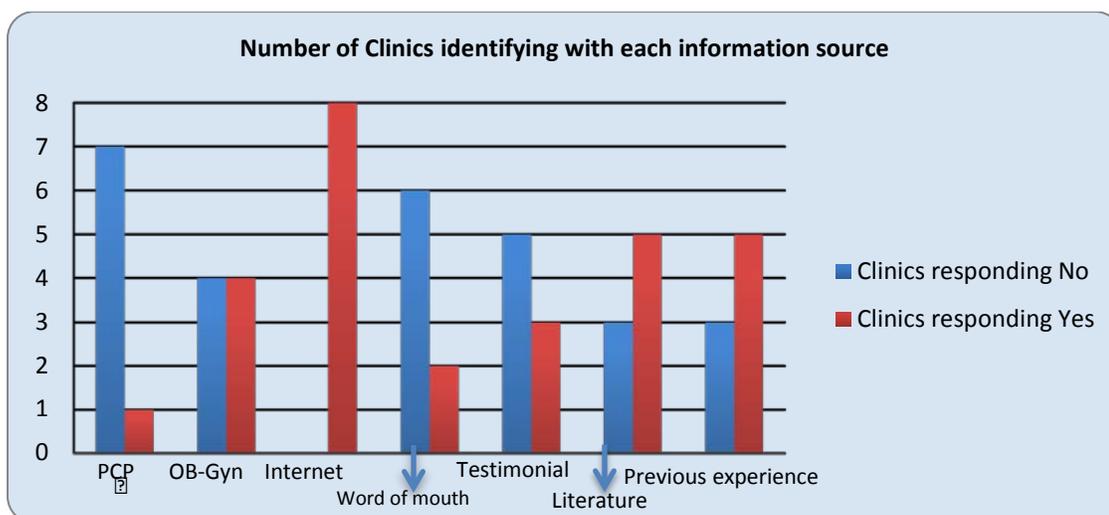


Figure 5. With eight of nine clinics responding, the initial information sources used by the clinics' current PGD/PGS patient base.

Referral patterns

The clinics described the ways in which their PGD/PGS patients were referred to clinic for counseling and the procedures. The majority was from Obstetrician-Gynecologist (OB-Gyn) and PCP information, with also a large number of no referral or walk-in patients (see Figure 6).

Despite the Ob-Gyn and PCP's prominent roles in overall referral, clinics were mixed in their opinion on whether PGD/PGS should become a more routine part of these physicians' referrals for potential parents within their patient populations.

What was interesting is that no clear pattern emerged between those whose patients had been referred from these sources and the clinics that did not believe the referral for PGD should be more routine. Some clinics that reported referrals from both PCP and Obstetricians or from one or the other stated that referrals from those sources should not be integrated more often. All clinics affirming the incorporation of pre-implantation genetic testing more routinely as a part of primary care referrals have had referrals from one or both of these sources in the past.

An attempt at clarifying the reason for the clinics' various answers with the follow up question of whether making PGS/PGD

referrals more routine would in fact unnecessarily overwhelm Assisted Reproductive clinics produced the following:

Four of the five clinics that did not support routine referrals for PGD also stated that they thought the clinics would be overwhelmed by the increase in patients seeking PGD from these PCP and OB-Gyn physician referrals (Table 7).

Of all four clinics stating that preimplantation genetic testing should become a routine reason for referral from primary care providers, all four stated that they did not believe the increase in patient demand would unnecessarily overwhelm clinics providing assisted reproductive care.

Interestingly, two clinics suggested increasing advertisement by either physicians or other healthcare providers but not both. Also, all 5 clinics that recommended increased public media education of PGS/PGD also supported increased advertisement and education by both physicians and other healthcare providers, as Table 8 indicates.

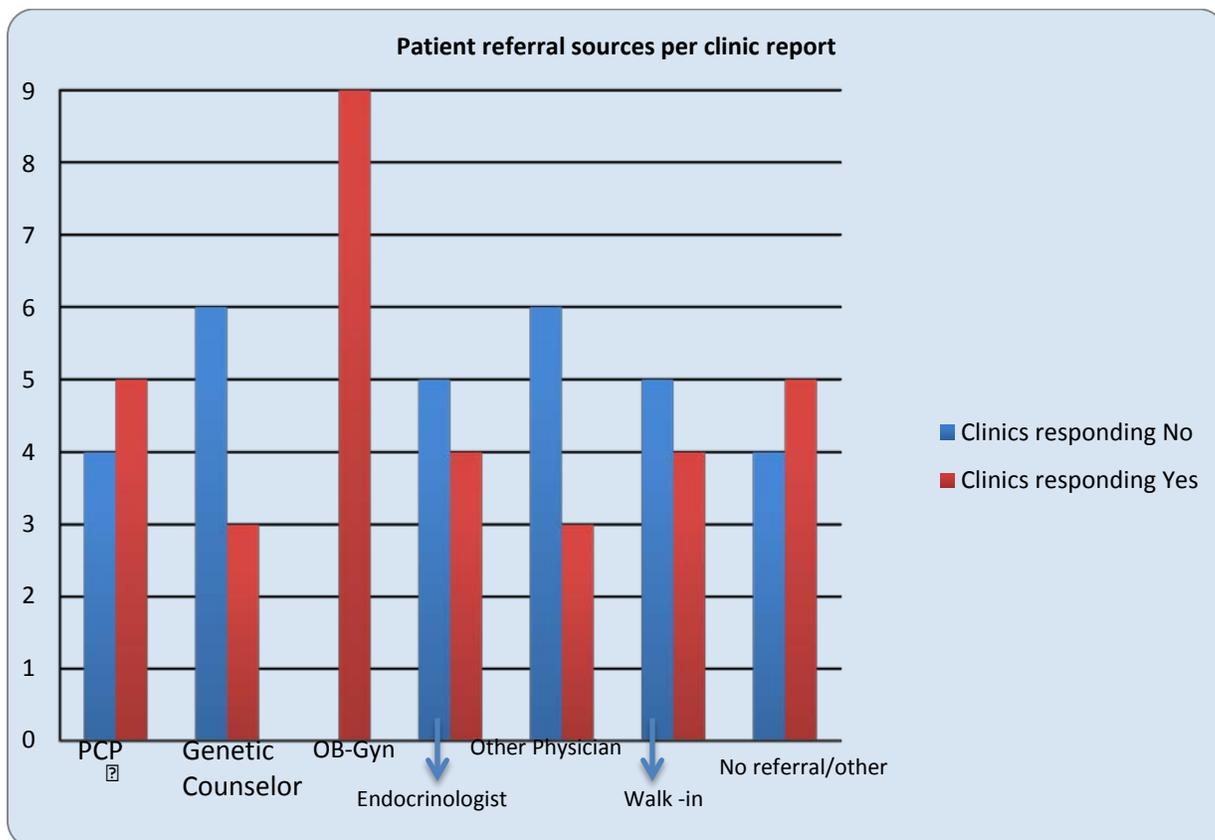


Figure 6. A look at the sources for patient referral to IVF clinic for preimplantation genetic testing. The Y axis constitutes number of clinics responding, the comparison is between those which said referral did not come from a specific entity (blue columns) and those that said it had (red columns). The X axis describes each of the sources, allowing for the comparison.

Should PGD be routine part of PCP/OB referrals?	Number of clinics responding
No	5 clinics
Yes	4 clinics

Table 7. Comparison of clinics responding to PGS as potential element of routine referral

Preimplantation genetic testing to be more widely advertised?	Yes	No
By Physicians?	6 clinics	3 clinics
Other healthcare providers?	6 clinics	3 clinics
Public media, press, internet?	5 clinics	4 clinics

Table 8. Clinics' suggestions for increased advertisement for PGS.

Increased Legislation or oversight

Eight of the nine clinics recommended that when any clinician has patients who are genetically-at-risk as parents, that they be required to inform them of either PGS or PGD. The one clinic which did not think such a requirement was necessary was also the clinic that did not think more routine preimplantation genetic testing referrals for parents with a presumed high risk of genetic disease, was necessary, or that wider advertisement from any of the groups in Table 8 would be helpful.

In regard to if IVF clinics providing PGD would benefit from increased regulation from outside sources, such as an accrediting body or the US government, IVF, the Arizona clinics were mostly in agreement, as demonstrated in Table 9.

The clinic responding that increased regulation would be helpful also responded that currently there is not enough regulation regarding sex selection, and also gave answers in support of increased advertisement, informing more patients of the possibility of PGD.

The final issue addressed by the survey was a follow up on the above question, and the clinics were definite in their responses that increased regulation from an outside source would not aid or promote

the development, growth and further use of the PGS/PGD testing services that these IVF clinics currently offer. Only one clinic declined to give an opinion.

Would IVF clinics benefit from increased regulation of PGD?	Number of clinics responding
Yes-very much	1 clinic responding
No-not at all	4 clinics responding
Minimal benefit or no opinion	4 clinics responding

Table 9. Clinic views on increased regulation for IVF clinics offering genetic testing

Discussion

As the results indicate, much demographic level data and clinic opinion of interest was gotten from the survey included. Larger significance will be seen in what follows.

to the background and the goals of the survey. Our interest with this study concerns the ramifications of PGD as it currently stands: be they social, ethical, political and regulatory, or medical—related to patient accessibility and practicality. And from the clinic data elicited, we are confident that these Arizona IVF clinics providing PGD offer an answer to some of the long-standing questions at work in the field.

First, in regard to patient numbers and interest, there is diversity of opinion. On the one hand, there is proven success and clinical evidence that PGD is beneficial when applied to high-risk groups. Yet has the benefit equaled the challenge of using the procedure, and the potential for IVF cycle failure? Pregnancy rates have gone up in some groups, but many patient studies of advanced maternal age or unexplained recurrent miscarriage have mixed results (Vissenberg 2011, Munne 2005, Preimplantation Genetic Testing: a practice committee opinion 2007). Are patient numbers increasing and

is the benefit to the IVF/non-diseased birth-rate as real as it seems from literature? Concerning pure numbers, from the reports mentioned earlier in this paper, there continues to be an increase in usage of both IVF and subsequently PGD, to the extent that now 1% of all US pregnancies are accomplished using IVF, and that 40+% of IVF cycles utilize PGD. Further, from Dr. Verlinksy's report on PGD in 2004 with over 1,000 successful pregnancies, to Dr. Simpson's report in 2011 of more than 10,000 PGD babies, the speed of growth is quite apparent. There is a ten-fold increase in just seven years—and this does not include the many PGD cycles that are not successful (only 20% are, see Reproductive Health Technologies Project 2011, "Preimplantation Genetic Diagnosis"). In light of these patient numbers, the number utilizing PGD in Arizona clinics is surprisingly small. Moreover, the age of the individual clinic correspondence to number of patients was only somewhat predicted, in terms of the number of PGD cycles performed.

It would be expected that the older clinics with PGD technique and abilities would have experienced much of the rapid increase in the past ten years. Two of the oldest clinics, founded in the mid-1990s did report the comparably larger numbers, but a clinic still older than

those had significantly fewer PGD patients. Further, the newest clinic had number 3 times those of clinics established years prior. It is unclear what the reasons are behind the low patient volume in Arizona. Possibly, the two non-responding clinics have higher numbers correspondingly, and then it might explain why many of the other IVF clinics had such small volume. Again, the volume shortage may link to the time in which most clinics were founded in Arizona, presumably because almost all were founded in 1994 or after—4 years after first successful PGD case—that the rate of growth in usage is at a much less exponential rate than at clinics where IVF had been provided already. A third reason for Arizona’s dearth of PGD numbers could also lie in the political and cultural context that exists more strongly in this state than in others. Consider the Arizona State Legislature House Bill as a case study, mentioned in the introduction. It is only one of several pieces of legislation that the Arizona Legislature has sought to pass, enumerating and at times abrogating the scope of reproductive access within the state. For instance, the worry from the legislature regarding sex selection, led to a push to ensure that any elective termination of a fetus is not tied to a motive to select the sex of the fetus, for family balancing or other reasons. The ease of

applicability of this abortion restriction to PGD's ability to sex-select, along with PGD clinics' willingness to do so for social or non-medical reasons, may provide a dampening effect upon the patient population seeking preimplantation genetic testing. Perhaps the long-term effect of such an active State Legislature is enough to decrease the interest in PGD services within the state. To further elucidate the clinics' experiences with this, a follow up survey is needed.

Then again, perhaps the explanation of numbers lies in the difference between the theoretical view of PGD and the 'clinical view', as described by Zeiler in her 2007 provider survey of PGD practices. The difference here would be in the effect of the economy on PGD growth in places that may not be the PGD hubs such as Chicago, New Jersey or New York, which have been burgeoning hubs for PGD development. In fact, the clinics implied as much when describing the volume of PGD patient growth during the same period of economic difficulty, with the majority's experience as business rising then falling, and only a third seeing steady growth during the same period.

With respect to the question of what, if anything, constitutes necessary regulation of PGD, both in terms of technique, and in terms of patient access to PGD, is of great interest, especially because, as

Cooper and Jungheim and others point out, there is much freedom for the IVF provider and the patient to ultimately determine use of the procedure (Cooper 2010). The US has little formal governmental oversight for assisted reproductive technology as it relates to preimplantation genetic testing, compared to European countries. Societies such as ASRM and SART (Society for Assisted Reproductive Technology) releases practice guidelines, but ultimately the use of genetic counseling and physician-patient decision making drive PGD utilization. Concerns for restriction in some places and leniency in others oversight include the possibility of “reproductive tourism” as Cooper calls it, which could drive up prices and prevent genetically at-risk patients unable to afford PGD from accessing the testing, by limitations in some areas of PGD activity, forcing patients with the means to seek PGD where the laws are more lenient. The worry is that such disparity in access could lead to genetic disease becoming a stigma relegated to the lower socio-economic classes who are unable to access PGD resources (Reproductive Health Technologies Project).

In our study, the concern for further oversight was prevalent, with all clinics agreeing that increased outside regulation would not promote the growth of PGD and its patient access. And on the whole

the clinics imparted a general satisfaction regarding the current state of minimal regulation, which, from much of the literature, including Cooper 2010, appears to be a sentiment nationally among clinics. However, some clinics did see the use of external governing body for standardization of specific applications of PGD, specifically sex selection. Interestingly, the clinics most emphasizing the need for regulation were among the larger providers of PGD in the state. This variance in clinic opinion on standardization of sex selection was remarkable, especially since one of the clinics adamantly opposed to providing sex-selection for non-medical reasons did not think additional standardization of the application is needed. Surprising, because that would be the assumed reason for why sex-selection standards may be needed, to rule in or rule out its use for family balancing. Perhaps the standardization desired relates to which patients requesting non-medical sex-selection should be provided PGD. Essentially, since little regulation exists beyond a recommendation toward minimizing non-medical sex selection, the clinics are currently on their own to primarily determine appropriate application of this and all other genetic testing that they provide. The reasons clinics differ in regard to this would provide for excellent follow up study.

On the outset of the study, an additional goal was entertained, that of understanding accessibility, beyond actual patient numbers, to the economics behind which patients could afford IVF and PGD. Specifically, within Arizona, the larger Hispanic and Native American populations stimulated the question did this different mix of patient populations lead to more diverse patient access to PGD. Granted, the white non-Hispanic population of Ashkenazi Jew, and other non-Hispanic Whites of European ancestry (carriers of Cystic Fibrosis, for instance) background could be a large percentage regardless of area of the country, on account of the nature of their genetic disease carrier rates. Yet, the question was, did a larger number of Hispanics and Native Americans seek PGD, in proportion to the larger population concentrations within Arizona? The answer came back that in fact, these populations were quite small. One clinic did report a large proportion of their patient base being Hispanic white, causing them to outstrip the proportion of African Americans seeking PGD. However, when comparing the percentages of Hispanics from all clinics, the overall approximate is 19% of patients seen by reporting clinics are Hispanic, Non-White. This percentage is two thirds of the percentage of Hispanic, Non-Whites in the Arizona population as reported by the

United States Census (that percent is 29.7%). Therefore, the Hispanic population was represented but not in proportion of the population, as reported by the clinics. This could speak to cultural differences or financial considerations or lack of education in regard to the utilization of preimplantation genetic testing. Furthermore, not a single clinic reported a Native American patient seeking PGD. That in itself could be a mix of reasons, however, and may also relate to their religious background. One of the clinic intimated that no patients with Native American traditional beliefs had been seen, but it was unclear if that was on account of the beliefs themselves or due to a lack of access.

Tied to the question of patient population access, is that of economic provision or lack thereof. Unsurprisingly, few clinics reported outside assistance for the PGD patients they have. No governmental assistance was mentioned, and only 2 clinics had patients with insurance coverage—fractions of their total patient population. There are some health insurances that provide assistance with PGD for proven genetic carriers, among other stringent criteria, while preimplantation genetic screening is less likely to be covered (Cigna Medical Coverage Policy, 2008). Yet since only a fraction of patients are covered, and the cost when combined with IVF is prohibitive,

clearly accessibility is an ever-present concern, at least for Arizona patients. With changes to governmental healthcare coverage provide assistance in this area, or will the amount of expense for IVF PGD cycles be seen as not practical, because of the limited success rate of pregnancies in high-risk patients even with PGD. If that occurs, then access may remain restricted, until improvements in technique and success rates can convince both insurance companies and the government that the dividends are worth the investment. This was what one of the clinics implied with their statement that insurance should cover PGD costs if the live birth rates increase and the number of multiples decrease.

Finally, the question of ethical concerns, looming large in much PGD literature, was explored with this study. Questions of family balancing via non-medical sex selection arose, and the results were remarkable. All responding clinics stated that they provided sex-selection, while seven clinics stated that they did not withhold embryonic sex information even for non-sex related diagnoses. Two reported that they withheld sex information if the disease under consideration were not sex-related or x-linked. The clinics also differed, as mentioned above, on the degree of standardization and regulation

tat would be helpful. Even in the context of a simple survey, the questions on sex-selection elicited tentative and guarded response. The clinics seem eager to keep the decision to use sex-selection within their own practice decisions, for the most part.

One of the early theories and arguments for promoting PGD was that it would save parents carrying known genetic disease the heartache of either not conceiving because of the risk of having an affected child, or of conceiving and then terminating once prenatal diagnosis confirmed the fetus's disease during the pregnancy (Zeiler, 2007). The hope was to cut down on the number of abortions by diagnosing affected embryos before implantation and then only implanting non-affected embryos. The clinics were asked about the actual clinical experience with this solution for genetic disease carriers, and their response was mixed, but so also are the patient populations seeking PGD—not all are known genetic carriers, some have only advanced maternal age or are uncertain of their genetic status. However, a majority of the clinics did note that at least some of their patients acknowledged using PGD as a measure to avoiding elective termination later in the pregnancy. Three clinics did not think that their patients had this reason. Associated with this is the patient

expectation of healthy babies as an expected outcome of PGD: an overwhelming 8 of the 9 responding clinics stated that their patients had this expectation. This confirms the question that many have of the inaccurate picture many patients have of PGD and its ability to diagnose and promote live, healthy pregnancy (Lavery 2004, among others), oftentimes because of a gilded image of success given in the media. Yet it was not apparent in this study that the clinics were concerned by the affect of external information sources upon the patients seeking their services. In fact, the vast majority would prefer that public education continue to provide education to the patients, but also saw the benefit of information coming from an Obstetrician or Primary care provider, perhaps to provide a counter-balance of the reality of PGD's limited success.

Interestingly, the question of HLA sibling matching elicited minimal response. Clinics have not seen much interest in this application of PGD, one that is debated fiercely on whether it is ethically or socially acceptable to utilize. Only clinics only had seen patients even interested in the use, and only one of the larger patient clinics reported providing PGD for that use. Yet this is not surprising, considering the small fraction of patients who would have a child

requiring this, yet the use and demand could grow, if the ethicality would be decided and patients see it as warranted. Additionally, the huge question of psychological affect on the matched sibling, growing up with the knowledge of being selected to help her sibling--this question would need an answer from the already-matched siblings.

Speaking to the survey itself, its strength lay in obtaining clinic data as quantitatively as possible, walking a fine line between an oral discussion with each clinic, and rigid, non-defined categories. Using a survey format that utilized free text comments but also multiple-choice questions, allowed for facile numerical comparison and reporting because the sample size was manageable. Thus the forced approximation of clinic responses into several categories made the experiences reported and the individual clinic data demonstrate more correlation and meaning when compared to each other. For the kind of data and the subject pool size, the survey struck a balance of a quantifiable descriptive study.

Also, the study was remarkable in its diversity of responses, as well as the overall response rate from the clinics. The IVF clinic community in Arizona was well represented with a large and satisfactory response rate, 9 of 11 total clinics, with one clinic

responding twice. Thus, the statistical robustness of the complete representative sample was satisfactory, because while the actual number of clinics is not high, the representative power of them as the entire group within Arizona was remarkable. Therefore the results and the statistical correlations were meaningful, in large part due to the nature of the surveying method utilized. It was discovered during the course of performing this study that for a sample size such as this one, contacting each clinic by telephone prior to their receipt of the survey tool, to notify them of the arriving survey and to explain the importance of the survey, was of vital assistance in ensuring a large proportion of clinics provided the overall PGD numbers for the state. A final response rate of 82% (excluding an apparent duplicate) for a mailed survey tool is impressive and correlated quite strongly with the general willingness noted during phone conversations with each clinic. Therefore, it is felt that the method of contacting the subjects in this survey study by two different means, telephone and mail, contributed strongly the results obtained.

In regard to the data from the clinics, there are two notes to be made regarding inclusion and omission of clinic results. First, as mentioned earlier, one of the clinics appeared to reply twice to the

survey, once during the primary mailing and again after the reminder survey mailing. When comparing the self-reported number of PGD/PGS patients, the numbers were almost identical and distinctly higher than most other reporting clinics, and the year of their clinic opening was the same. Both of these answers, when combined with the surveys responses to patient financial data and demographics, demonstrated a unique pattern consistent between the surveys and dissimilar from enough from the rest of the clinics' responses. As a result, these surveys were presumed to originate from the same clinic via different clinic respondents. Their answers were then combined and used to represent one clinic's response only, using the clearest replies from either. For the two surveys' opinions regarding PGD practices and usages, the responses were extremely close, speaking to the responders from the clinic being either 1. the same person or 2. the respondents faithfulness in filling out the survey as a response from the clinic and not just as an individual working at the clinic. Additionally, it was interesting to note that the first of the two similar surveys did actually self-identify, despite our repeated emphasis both in writing and orally to return the surveys without any identifiers. All

ten other returned surveys were anonymous, including the second survey apparently from the same clinic.

The second note to be made is in regard to the other clinic with high patient volume reported, specifically, the one reporting a presumed PGD patient number of approximately 1000. Clearly, this number was quite high in comparison to other reporting clinics, over 900 patients more than the next highest reporting clinic. In the survey question for patient number, the number of PGD/PGS patients diagnosed at the clinic was specifically asked. However, based on the responses from every other clinic, including those opened in the same year or even earlier, there was no other clinic reporting patient numbers at all correlating with this clinic's. In discussing with both the study mentors and a statistician, it was thought that the question might have been misread and the patient number was reporting entire IVF patients or cycles, instead of just those patients who additionally utilized PGD or PGS. Or, it is possible that the patient totals reported was indeed the accurate number of PGD patients seen by the clinic. For instance, the clinic might be associated with a major university or health provider group, thereby attracting larger patient numbers. Ultimately, we wanted to include the clinic's reported data with the

second possibility in mind, but also reported overall statistics from all the clinics, while excluding this clinic's number, because the reporting mean and range changed substantially with this aberrant data point, obscuring the more clustered but much smaller patient totals from other clinics. Thus, the clinic was included in all other calculations and tables with regard to the rest of the survey questions, but was distinguished from the others in patient numbers and numbers in terms of clinic years. In this way, we could preserve accurate statistical reporting from the other clinics but not reject this seeming variant piece of clinic data entirely.

Future Directions

In many ways, this survey provided clarity and insight into the world of IVF clinics and current use pre-implantation genetic testing, and yet raised many more questions. The survey has recognizable strengths and weaknesses, both in what was asked, and also in how the survey questions were worded and the ability to convey the material we desired to know. At several points, the questions were vague and allowed for misinterpretation by the clinics, as a result, some answers had to be regrettably handled lightly and with data left unexplored, because while insightful, it was not correlated with the rest of the clinic data presented. In the future, a more specific survey, building on the demographics data and opinions discovered in this survey, would be enlightening. By using the same model as this survey, providing a quantifiable structure to a qualitative and important discussion of specific clinical experience, it would allow for reportable comparison of clinics, but at the same time expand the meaning and elucidate some of the answer to this current survey. In terms of specific alterations these some recommendations: utilizing more precise language with regard to the genetic testing, and asking about sex-selection in more defined terms of involving family balancing

versus solely for x-linked disease identification, as well as using more succinct and meaningful jargon when asking opinions on oversight and patient communication.

Furthermore, it might be helpful for such a correlated survey to include more specifics about the genetic studies each clinic has done, and their success rates and patient satisfaction, more personalized responses than the general ones focused on in this study.

Additionally, the study was limited by the size of its subject pool, which although it gave a substantial report from a statistically complete pool, nevertheless the study is limited by its intentional circumscription. The breadth of exposure that a survey involving clinics from several states or nationally could allow for further generalization than this study, limited by regional demographics and experiences, could wisely be able to impart. Thus a wider study using the same survey methodology would be an excellent follow up, even if it might be time-consuming.

Conclusion

The response of the clinics, at many points, correlated with national and current opinion, regarding regulation and growth. The survey highlighted the relationship of the referring physician and the Arizona PGD patient, and characterized the patient population for those seeking PGD in Arizona. It is hoped that this data will be utilized to inform local PGD clinics and the national PGD community where to focus their efforts in promoting realistic and understandable information about what PGD offers as well as the limitations of the techniques. Knowing that the primary sources of information about PGD is through Internet searches and the media, a concerted effort can be undertaken by the PGD community to improve the accuracy of information available from these sources.

With respect to regulation of PGD practices, the discussion of sex-selection for non-medical reasons is currently one addressed by each clinic separately in the state of Arizona. The regulation of sex-selection remains a controversial issue and debate in this area continues. Yet, evident in the results from these clinics, is the need to let clinic experiences and opinions inform the discussion. A larger survey of clinic opinion, asking in what ways sex-selection should be

standardized and when, would be helpful and could lead to agreement about standard procedure.

Finally, the issue of limited accessibility in minority populations was illustrated again in this study, with the caveat that the Arizona patient population mirroring the local population rates to a minor extent. Yet, the obvious economic inhibition remains, and may only change as PGD becomes more thorough and affordable.

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