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ARTICLE

PGD for all cystic fibrosis carrier couples: novel strategy for preventive medicine and cost analysis

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Abstract Over 1000 children affected with cystic fibrosis (CF) are born annually in the USA. Since IVF with preimplantation genetic diagnosis (PGD) is an alternative to raising a sick child or to aborting an affected fetus, a cost–benefit analysis was performed for a national IVF–PGD program for preventing CF. The amount spent to deliver healthy children for all CF carrier-couples by IVF–PGD was compared with the average annual and lifetime direct medical costs per CF patient avoided. Treating annually about 4000 CF carrier-couples with IVF–PGD would result in 3715 deliveries of non-affected children at a cost of $57,467 per baby. Because the average annual direct medical cost per CF patient was $63,127 and life expectancy is 37 years, savings would be $2.3 million per patient and $2.2 billion for all new CF patients annually in lifetime treatment costs. Cumulated net saving of an IVF–PGD program for all carrier-couples for 37 years would be $33.3 billion. A total of 618,714 cumulative years of patients suffering because of CF and thousands of abortions could be prevented. A national IVF–PGD program is a highly cost-effective novel modality of preventive medicine and would avoid most births of individuals affected with debilitating genetic disease.

KEYWORDS: assisted reproductive technology, cost–benefit analysis, cystic fibrosis, in-vitro fertilization, national health, preimplantation genetic diagnosis

Introduction

Cystic fibrosis (CF) is the most prevalent, life-shortening, inheritable disease amongst Caucasians in the USA (Grosse et al., 2004). The carrier frequency is about one in 25, and about one in 3700 babies born in the USA are affected (Asch et al., 1998; Grosse et al., 2004; Krauth et al., 2003; Wald et al., 2003). If both parents are carriers (+/+ CF couple), there is a 25% chance that a child will be affected. Despite significant improvements in treatment, CF

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still remains an incurable, severe and costly disease. The median age of diagnosis is 5.3 months (American College of Obstetrics and Gynecology [ACOG], 2001) and the current life expectancy in the USA is 36.7 years (CF Foundation, 2007; Dodge, 1999; Wilcken and Travert, 1999).

In 1989, CF was recognized to result from mutations in the cystic fibrosis transmembrane conductance regulator gene (Amos and Grody, 2004). This gene has been characterized, making it possible to identify affected individuals. Years ago, newborn screening was introduced to improve health outcomes and quality of life for children born with CF (Lee et al., 2003; Wilcken and Travert, 1999). More recently, preconception carrier screening of parents and prenatal testing was implemented to prevent the birth of CF children and is currently recommended by the ACOG and American College of Medical Genetics (ACOG, 2001; Grody and Desnick, 2001; Grody et al., 2001; Vintzileos et al., 1998). Nevertheless, there are still more than 1000 babies affected with CF born each year in the USA (Grosse et al., 2004; Lee et al., 2003) and the total direct medical costs spent each year treating CF patients was more than $1.3 billion as of the year 2000 (CF Foundation, 2007).

Several reproductive options are available to +/+ CF couples (Chamayou1 et al., 1998; Henneman et al., 2001; Pergament, 1991): (i) accept the risk of conceiving a child affected with CF; (ii) undergo prenatal diagnosis, with or without the possibility of terminating an affected pregnancy; (iii) decide against further pregnancies; (iv) adoption or using donor gametes; and (v) preimplantation genetic diagnosis (PGD) in conjunction with IVF to ensure the birth of a healthy child unaffected with CF. While population screening for CF with elective termination of pregnancy has been clearly shown to be cost effective (Vintzileos et al., 1998), the screening—termination approach has significant drawbacks, primarily because many patients would prefer not to face such a decision because of ethical or religious considerations (Chamayou1 et al., 1998; Henneman et al., 2001; Pergament, 1991). Studies of patients' attitudes towards reproductive options revealed that about 50% of high-risk women for genetic disorders with previous experience of prenatal testing would prefer PGD for the next pregnancy (Chamayou1 et al., 1998; Pergament, 1991). Moreover, in couples who experienced previous therapeutic abortions following prenatal testing, the percentage of those who prefer the PGD alternative, increased to 72% (Chamayou1 et al., 1998). One of the most important questions is how many couples would opt to choose PGD over prenatal diagnosis (PND). In order to answer this specific question, Musters et al. (in press) investigated the preference for PGD as an alternative to PND in a large group of couples with genetic disorders. Of all 960 valid questionnaires returned, 407 couples were in their reproductive years (18—40 years old). Of the 210 couples who did want to conceive, 74% of these couples preferred testing with PGD. When PGD could be performed without any significant delay, 80% preferred PGD over PND. In this new study (Musters et al., in press), the preference for PGD (74—80%) is higher than previously reported (30—72%). This higher preference for PGD could be because other studies on these topics were performed more than a decade ago, at that time IVF—PGD was not as accepted. IVF is now an established and accessible treatment, reimbursed by some health insurance companies. In the current study, couples were approached by researchers who were not part of a clinic offering PGD, as in prior studies. Therefore, this study better represents the group as a whole.

Reluctance to terminate a pregnancy may be a major reason contributing to the continuing birth of more than 1000 children affected with CF annually in the USA (Chamayou1 et al., 1998; Henneman et al., 2001; Lee et al., 2003; Pergament, 1991), and therefore, a better preventive strategy should be considered. Preimplantation genetic diagnosis (PGD) is a modern modality of preventive medicine and can now be used to identify embryos affected with CF prior to transferring them into the uterus (Handyside et al., 1992; Strom et al., 1998; Verlinsky et al., 1992). PGD is performed in conjunction with IVF and, if used by all +/+ CF couples, has the potential to prevent the birth of new children affected with CF. For most couples at risk for passing on genetic diseases to their offspring, PGD is a preferred option compared with aborting an affected fetus or raising a sick child. The objective of this study was to examine the cost—benefit of using PGD to prevent the birth of children with CF by comparing the cost of IVF—PGD for all +/+ CF couples to the direct medical costs saved by preventing the need to treat new CF patients.

Materials and methods

A comprehensive evaluation of the actual annual cost for the care of patients with CF at the Cystic Fibrosis Centre at Lutheran General Hospital (LGH), Park Ridge, IL was conducted for 2006. During that year, 66 CF patients, aged from birth to 35 years old (mean age of 18.3 years), were treated at LGH, as in- and out-patients. Payer mix was: 38% preferred provider organizations, 34% health maintenance organizations and 28% Medicaid. All actual billings of hospital and clinic charges directly related to the treatment of complications of CF were collected from administrative records. Medications' charges were based on the retail prices reported by CF-specialty pharmacies multiplied by the actual use of the medications by each patient as reported by the patient/parents. The CF costs mentioned above include only the extra treatments that a CF patient requires. All the other non-CF related costs (e.g. immunizations, regular paediatric follow-ups) were assumed to be similar between CF and non-CF patients. The average direct healthcare expenditures for treating one patient with CF, without lung transplant, at the CF centre at LGH during 2006 was $63,127 and this figure was used here for the cost—benefit analysis. The data were comparable to the US Cystic Fibrosis Foundation's estimated annual direct medical expenditures of treating CF patients for the year 2000 of $55,537 (CF Foundation, 2007).

During 2000—2005, the Reproductive Genetics Institute (RGI) in Chicago, IL, performed 104 PGD cycles for 74 +/+ CF couples who wished to avoid the conception of children affected with CF. **Table 1** summarized all consecutive IVF—PGD cycles performed on +/+ CF couples where the women's age was less than 42 years. With IVF—PGD, 75% of the embryos will either be unaffected (−/−) or CF carriers (+/−) and, therefore, are suitable for transfer. While transferring only non-carrier embryos (−/−) might dramatically reduce the prevalence of CF carriers in the population

Table 1 Outcomes of IVF—preimplantation genetic diagnosis (PGD) cycles for cystic fibrosis (CF) (2000—2005).

Parameter	*Value*
No. of patients (age ≤42 years)	74
No. of cycles for PGD for CF	104
Mean no. of IVF—PGD cycles/couple	1.4 (104/74)
No. of cycles with embryo transfer (%)	94 (90.4)
No. of embryos transferred	184
Mean no. of embryos transferred	1.96 (184/94)
Total number of pregnancies	44
No. of miscarriages (%)	7 (15.9)
No. of deliveries	37
No. of healthy babies born	49
No. of babies per delivery	1.3
No. of cycles resulting in pregnancy (%)	44/104 (42.3)
No. of transfer cycles resulting in a pregnancy (%)	44/94 (46.8)
Take-home baby rate per IVF—PGD cycle (%)	37/104 (35.6)

(and may be the preference of some patients), transfer of embryos that are CF carriers (+/—) is ethically acceptable and is routinely performed. A successful outcome was judged as a birth of at least one live-born child, not affected with CF, as defined by the take-home baby rate per treatment cycle (**Table 1**).

The approximate expenses for the initial and subsequent IVF—PGD treatment cycles were derived by combining estimated average costs for IVF in the Midwest and for PGD at RGI during 2004—2005 (**Table 2**).

Using IVF—PGD as a strategy for reducing the number of children born with CF presumes that an effective

Table 2 Estimated cost of IVF—preimplantation genetic diagnosis (PGD) treatment for cystic fibrosis (CF) carriers.

Procedure		*Cost (US$)*	*Notes*
IVF	Pre-IVF laboratory screening	1000	Range $600 to $2000; needs to be performed only once each year
	Medications[a]	3000	Range $1500 to $5000
	Cost of IVF treatment cycle[b]	12,000	Range $6000 to $18,000
	Total cost, first IVF cycle	16,000	
	Total cost, each additional IVF cycle	15,000	
PGD	Genetic system set-up for PGD of a specific couple[c]	1500	Range $1000 to $2000; performed once for a specific couple, with or without analysis of second generation, if applicable
	Biopsy of oocytes and embryos	1500	
	Genetic analyses of oocytes by polar bodies biopsy and embryos by blastomere biopsy	3000	Variable; upper end presented; depends on number of mutations anticipated
	Subtotal: cost of PGD, first cycle	6000	
	Subtotal: cost of PGD, each repeated cycle	4500	
IVF—PGD	Total cost, first IVF—PGD cycle	22,000	
	Total cost, each additional IVF—PGD cycle	19,500	

[a]Estimated from average purchase of IVF patient including medications for ovarian stimulation, prevention of spontaneous LH surge and pregnancy support during first trimester.
[b]Includes blood tests, ultrasound monitoring, oocyte retrieval under ultrasound guidance with anaesthesia, embryology for identifying oocytes, fertilization by intracytoplasmic sperm injection, embryo culture to the blastocyst stage, transfer of embryos as blastocysts, etc.
[c]The genetic set-up for cystic fibrosis mutations applicable to a particular couple needs to only be performed once.

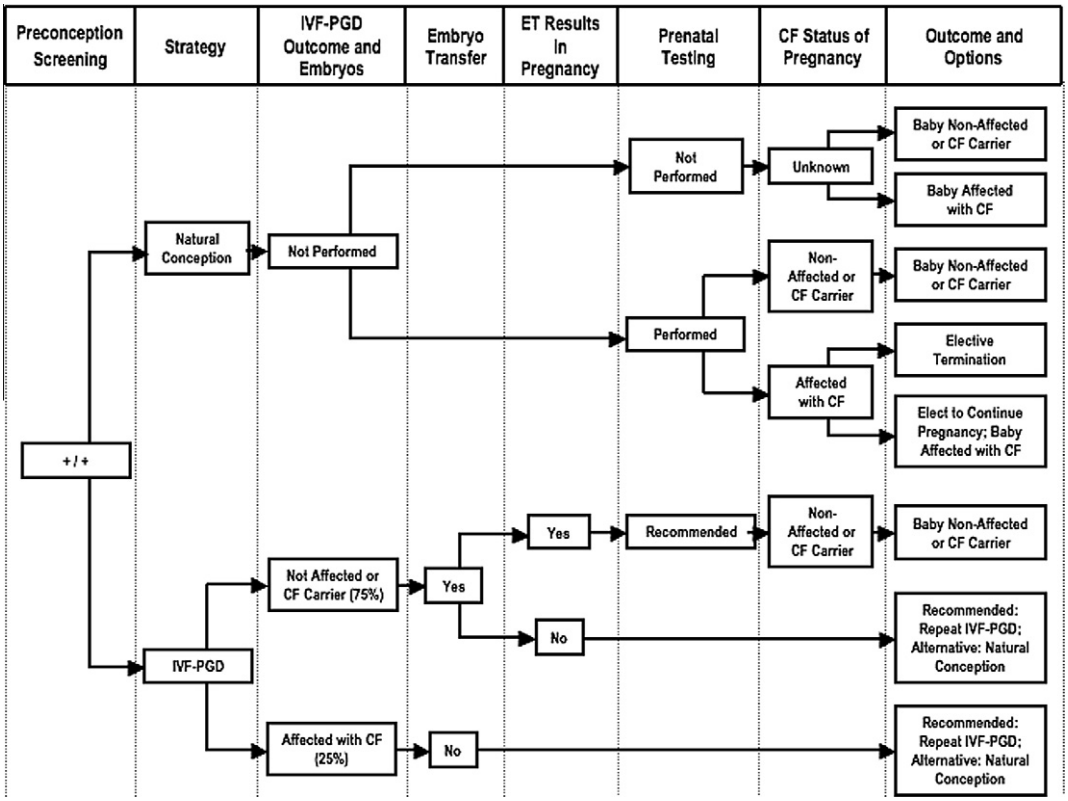

Figure 1 A decision-tree model used for clinical options available for carrier couples with CF who wish to conceive a healthy baby.

preconception screening program exists and that +/+ CF couples who wish to conceive are willing to undergo IVF—PGD. A decision-tree model was then constructed where the branches represent different strategies and potential clinical options or outcomes for carrier couples with CF who wish to conceive a healthy baby (**Figure 1**).

The cost—benefit analysis was performed in a step-wise fashion. The first step estimated the number of healthy children that would result from a comprehensive national IVF—PGD program given observed success rates and calculated total annual costs as well as cost per delivery (**Table 3**). Because CF is an autosomal recessive disorder, four couples would have to conceive a healthy child by IVF—PGD to prevent the birth of one affected child. The long-term annual and cumulative savings of IVF—PGD programme to circumvent the birth of children with CF was

Table 3 Estimated cost of performing IVF—preimplantation genetic diagnosis (PGD) on 4000 +/+ cystic fibrosis (CF) couples who theoretically would conceive 1000 babies affected with CF each year, assuming four deliveries of healthy children by IVF—PGD being needed to prevent the birth of one affected baby (25%) ($57,460 × 4 = $229,840).

IVF—PGD cycle number	*No. of cycles*	*Delivery rate (%)*	*Non-affected deliveries*	*Cumulative deliveries*	*Cumulative delivery rate (%)*	*Cost/ cycle (US$)*	*Total cost (US$)*
First	4000	35.6	1424	1424	35.6	22,000	88,000,000
Second	2576	35.6	917	2341	58.5	19,500	50,232,000
Third	1659	35.6	591	2932	73.3	19,500	32,350,500
Fourth	1068	35.6	380	3312	82.8	19,500	20,826,000
Fifth	688	35.6	245	3557	88.9	19,500	13,416,000
Sixth	443	35.6	158	3715	92.9	19,500	8,638,500
Totals	10,434		3715				213,463,000
Estimated cost per delivery of healthy baby			3715				57,460
Estimated cost per affected delivery avoided*			929				229,777

then examined (Table 4). The long-term analysis presumes that IVF–PGD would need to be performed on a fixed number of 4000 couples each year and that the cost saving would accrue about 1 year later (because of the length of a pregnancy). It compares the cost of IVF–PGD to potential savings derived from avoiding the need to treat new patients affected with CF over a period of 37 years which is the current life expectancy for a child born with CF (CF Foundation, 2007; Dodge, 1999). Note that the cost–benefit analyses presented does not include indirect costs such as loss of productivity and quality of life issues, which are quite significant.

Results

Costs of treating patients with CF

The average direct healthcare expenditures for treating one patient with CF, without lung transplant, at the CF centre at Lutheran General Hospital during 2006 was $63,127. This cost is comparable to the CF foundation data from 2000 of $55,537 (CF Foundation, 2007). With a life expectancy of 36.7 years (Dodge, 1999), direct lifetime medical expenditures for each CF patient are anticipated to exceed $2.3

Table 4 Annual and cumulative costs and savings resulting from implementing IVF–preimplantation genetic diagnosis (PGD) as a strategy to decrease the number of children born with cystic fibrosis (CF) (in US$ millions) assuming IVF–PGD prevents the birth of 929 babies affected with CF each year.

Year	*Annual cost/saving*			*Cumulative cost/saving*		
	IVF–PGD	*Projected saving in CF treatment expenses*	*Net cost/saving*	*IVF–PGD*	*Projected saving in CF treatment expenses*	*Net cost/saving*
1	(213.5)	0.0	(213.5)	(213.5)	0	(213.5)
2	(213.5)	58.6	(154.8)	(426.9)	58.6	(368.3)
3	(213.5)	117.2	(96.2)	(640.4)	175.9	(464.5)
4	(213.5)	175.9	(37.6)	(853.9)	351.7	(502.1)
5	(213.5)	234.5	21.0	(1,067.4)	586.2	(481.1)
6	(213.5)	293.1	79.6	(1,280.8)	879.4	(401.5)
7	(213.5)	351.7	138.3	(1494.3)	1231.1	(263.2)
8	(213.5)	410.4	196.9	(1707.8)	1641.5	(66.3)
9	(213.5)	469.0	255.5	(1921.2)	2110.5	189.2
10	(213.5)	527.6	314.1	(2134.7)	2638.1	503.4
11	(213.5)	586.2	372.8	(2348.2)	3224.3	876.1
12	(213.5)	644.9	431.4	(2561.7)	3869.2	1307.5
13	(213.5)	703.5	490.0	(2775.1)	4572.6	1797.5
14	(213.5)	762.1	548.6	(2988.6)	5334.8	2346.2
15	(213.5)	820.7	607.3	(3202.1)	6155.5	2953.4
16	(213.5)	879.4	665.9	(3415.5)	7034.8	3619.3
17	(213.5)	938.0	724.5	(3629.0)	7972.8	4343.8
18	(213.5)	996.6	783.1	(3842.5)	8969.4	5126.9
19	(213.5)	1055.2	841.8	(4056.0)	10024.7	5968.7
20	(213.5)	1113.9	900.4	(4269.4)	11138.5	6869.1
21	(213.5)	1172.5	959.0	(4482.9)	12311.0	7828.1
22	(213.5)	1231.1	1017.6	(4696.4)	13542.1	8845.7
23	(213.5)	1289.7	1076.3	(4909.8)	14,831.8	9922.0
24	(213.5)	1348.3	1134.9	(5123.3)	16,180.1	11,056.8
25	(213.5)	1407.0	1193.5	(5336.8)	17,587.1	12,250.3
26	(213.5)	1465.6	1252.1	(5550.2)	19,052.7	13,502.5
27	(213.5)	1524.2	1310.7	(5763.7)	20,576.9	14,813.2
28	(213.5)	1582.8	1369.4	(5977.2)	22,159.8	16,182.6
29	(213.5)	1641.5	1428.0	(6190.7)	23,801.2	17,610.6
30	(213.5)	1700.1	1486.6	(6404.1)	25,501.3	19,097.2
31	(213.5)	1758.7	1545.2	(6617.6)	27,260.0	20,642.4
32	(213.5)	1817.3	1603.9	(6831.1)	29,077.4	22,246.3
33	(213.5)	1876.0	1662.5	(7044.5)	30,953.3	23,908.8
34	(213.5)	1934.6	1721.1	(7258.0)	32,887.9	25,629.9
35	(213.5)	1993.2	1779.7	(7471.5)	34,881.1	27,409.6
36	(213.5)	2051.8	1838.4	(7685.0)	36,932.9	29,248.0
37	(213.5)	2110.5	1897.0	(7898.4)	39,043.4	31,145.0
38	0.0	2169.1	2169.1	(7898.4)	41,212.5	33,314.0

Costs are shown as values in parentheses.

million. Medical expenses vary with age and with severity of the disease (with or without the need for lung transplant). To keep the calculations relatively straightforward, the average annual direct medical expenditures without lung transplant of $63,127 was used in the cost–benefit analyses.

IVF–PGD success rates and costs

By the end of 2005, 74 patients had undergone 104 consecutive oocyte retrievals and PGD with RGI (a mean of 1.4 cycles per couple) (Table 1). Ninety percentages of those cycles yielded unaffected embryos suitable for transfer.

Overall, 35.6% of the IVF–PGD cycles yielded a life birth with one or more healthy babies. If IVF–PGD is not successful, the couple must decide whether to attempt another cycle of IVF–PGD (Figure 1) knowing that their probability of having a baby approaches 75% after only three treatment cycles and is predicted to exceed 93% after six treatment cycles (Table 3).

If 4000 couples undergo one cycle of IVF–PGD, 1424 deliveries with non-affected children are expected (Table 3). Assuming a similar success rate of 35.6% in subsequent treatment cycles and that couples could elect to undergo between four and six attempts per year yields a cumulative success rate approaching 93%. IVF as performed in the USA typically involves the transfer of two or three embryos. The series yielded 1.3 non-affected babies per pregnancy with an average of about two embryos per transfer (Table 1). Thus, the number of resulting children would be higher than the number of deliveries, perhaps by as much as 30% (Table 3). Nonetheless, to avoid multiple births, which have both medical complications and an additional cost, the outcome was calculated as if each delivery results in the birth of one non-affected child.

IVF–PGD cycles can be performed at an experienced centre. The estimated cost of performing the initial IVF cycle with intracytoplasmic sperm injection (ICSI) without PGD was $16,000 including laboratory and imaging screening, cost of medications, monitoring during ovarian stimulation and the IVF procedure *per se* (Table 2). The cost of subsequent IVF cycles was lower because the initial screening does not need to be repeated until a year later. Estimated PGD costs were $6000 for the initial cycle and $4500 for subsequent cycles. The cost for subsequent PGD cycles would be lower because the initial genetic set-up for couples (parents) and siblings for linked genetic markers and probes needs to be performed only once. These conditions yield an estimated cost of $22,000 for the initial cycle of IVF/ICSI–PGD and $19,500 for each subsequent treatment cycle.

Estimated costs and potential savings of using IVF–PGD versus the cost of treating patients affected with CF

Performing IVF–PGD on 4000 +/+ couples each year, with repeated attempts, would cost about $213.5 million (Table 3). This translates to an amortized cost of $57,460 per delivery of an unaffected baby. Because of the 25% chance that natural conception will result in a child affected with CF, four deliveries of non-affected children by IVF–PGD, at a cost of $229,840 ($57,460 × 4), are required to circumvent the birth of one affected child. Because the annual average expense of treating one CF patient (without lung transplant) is $63,127, the breakeven point of using IVF–PGD to prevent the birth of each affected child is 3.6 years ($229,840/$63,127).

For each baby that is delivered unaffected instead of being affected with CF, the average calculated lifetime net savings in direct treatment costs is $2,105,860 (treatment for 37 years = $2,335,699 − $229,840). The annual saving accrued by not having to treat 929 CF patients was estimated to be $58.6 million ($63,127 × 929). Over a life expectancy of 37 years, not having to treat 929 CF patients translates to a net saving of $2.17 billion in direct healthcare expenditures.

A long-term cost–benefit analysis, consisting of both annual and cumulative projections, is presented in Table 4. In terms of annual cost–benefit, the break-even point for a long-term IVF–PGD program for the USA occurs at 4.9 years. This is about 1 year longer than the break-even point for one patient because births occur about 9 months after treatment and the saving in healthcare expenses would start about 1 year after the program is initiated. Thus, examination of yearly projections for the fifth year reveals that investing $213.5 million dollar in IVF–PGD annually results in a net projected healthcare savings of $21 million (Table 4) and steadily increases thereafter.

The cumulative savings of a continuous program would reach the break-even point at 8.2 years (Table 4). Once about $1.7 billion have been invested in IVF–PGD, the projected net healthcare savings become positive. This 1.7 billion dollar investment over 8 years seems reasonable considering that more than $1.5 billion is currently expended each year in treating all patients affected with CF ($63,127 × 24,487 total registered US CF patients as of 4 September 2007). For example, after 37 years the implementation of IVF–PGD is projected to save about $33.3 billion in healthcare expenditures.

At the same time period, thousands of terminations of pregnancies of fetuses affected by CF, diagnosed by prenatal testing, would be prevented. By using long-term IVF–PGD programs, a total of 33,444 new CF births would have been avoided. Thus, 618,714 cumulative years of patients suffering because of CF could have been avoided after 37 years (Table 5).

Assuming about 50% reduction in the total number of +/+ CF couples that will elect to undergo IVF–PGD treatment (2000 instead of 4000) will still keep the positive cost analysis. There will be no delay in reaching the break-even point, and net saving is $14.2 billion.

Discussion

Large-scale implementation of IVF/ICSI with PGD at the national level, to prevent the birth of individuals affected with a life-shortening genetic disease, is a novel modality of modern preventive medicine, analogous to the role of vaccinations in preventing infectious diseases. The introduction of new health services is constrained by limited national healthcare resources. Therefore, a cost–benefit analysis is appropriate before new medical technologies or treatments are adopted. This study evaluates the potential benefits of

Table 5 Number of births of cystic fibrosis (CF) children circumvented each year and the cumulative treatment years, avoided for one and for all patients.

Year	Annual births		Cumulative births	
	No. of new CF patients avoided	Cumulative no. of new CF patients avoided	Cumulative treatment years avoided per one non-CF patient each year	Cumulative treatment years avoided for all non-CF patients
1	0	0	0	0
2	929	929	1	929
3	929	1858	3	2787
4	929	2787	6	5574
5	929	3716	10	9290
6	929	4645	15	13,935
7	929	5574	21	19,509
8	929	6503	28	26,012
9	929	7432	36	33,444
10	929	8361	45	41,805
11	929	9290	55	51,095
12	929	10,219	66	61,314
13	929	11,148	78	72,462
14	929	12,077	91	84,539
15	929	13,006	105	97,545
16	929	13,935	120	111,480
17	929	14,864	136	126,344
18	929	15,793	153	142,137
19	929	16,722	171	158,859
20	929	17,651	190	176,510
21	929	18,580	210	195,090
22	929	19,509	231	214,599
23	929	20,438	253	235,037
24	929	21,367	276	256,404
25	929	22,296	300	278,700
26	929	23,225	325	301,925
27	929	24,154	351	326,079
28	929	25,083	378	351,162
29	929	26,012	406	377,174
30	929	26,941	435	404,115
31	929	27,870	465	431,985
32	929	28,799	496	460,784
33	929	29,728	528	490,512
34	929	30,657	561	521,169
35	929	31,586	595	552,755
36	929	32,515	630	585,270
37	929	33,444	666	618,714

implementing IVF—PGD to prevent conception and birth of babies affected with CF. Based on a comparison to the direct medical treatment costs that would have otherwise been expended in treating those patients, offering IVF—PGD to all CF carrier couples who want to conceive a healthy baby is highly cost effective and has the potential to save billions of dollars in healthcare expenses. The potential implications of using IVF—PGD for +/+ CF couples are truly remarkable, both from an economic and personal perspective.

For the USA, investing about $213.5 million annually in IVF—PGD could circumvent the birth of most children affected with CF. Implementing an IVF—PGD program for 1 year will circumvent the birth of 929 new CF patients and will save, over a 37-year life expectancy, $2.3 billion in direct healthcare expenditures. The cost to avert each delivery of an affected baby was estimated to be $230,000, an average amount that is currently expended in about 3.6 years as direct healthcare costs associated with treating one person with CF. In terms of annual cost—benefit, the break-even point for a long-term IVF—PGD programme for the USA occurs at 4.9 years. This is 1 year longer than the break-even point for one patient because births occur about 9 months after treatment. Examination of yearly projections reveals that from the fifth year onward, investing $213.5 million dollar in IVF—PGD results in

a net projected healthcare savings that steadily increases (**Table 4**).

The cumulative savings of this program would reach the break-even point at 8.2 years. Once about $1.7 billion have been invested IVF–PGD, the projected net healthcare savings become positive (**Table 4**). This 1.7 billion dollar investment over 8 years is reasonable considering that currently more than $1.5 billion are expended each year in treating patients affected with CF. The cumulative projections for years 1–5 reveal that if the savings in treating new CF patients would be re-directed to IVF–PGD, a net investment of only $502 million would be sufficient to establish this program that would have profound long-term consequences. After 37 years, the projected net cumulative saving in healthcare expenses is about $33.3 billion.

Several assumptions were used to keep the cost–benefit analysis relatively straightforward. The primary benchmarks used were the average annual and lifetime costs of treating a person with CF as accumulated at the CF centre at LGH, which was comparable to that of the US CF Foundation. The direct medical costs associated with treating a particular CF patient vary considerably and increase with the severity of the disease as well as age (progression of the disease) and country (Krauth et al., 2003; Rowley et al., 1998; Simpson et al., 2005). If desired, the model could be modified to take into account severity of the disease or amortize direct medical expenditures according to the age of the patient. Under those modifications, the overall cost–benefit remains positive. For example, assuming about 50% reduction in the total annual cost of treating one CF patient ($30,000) will delay reaching the break-even point by about 5 years, but will still result in net saving of $11.7 billion.

Prenatal or preconception carrier screening for CF of parents was implemented in the last decade as a major strategy to prevent the birth of CF children and is currently recommended for most ethnic groups by the American College of Obstetrics and Gynecology and American College of Medical Genetics (ACOG, 2001; CF Foundation, 2007; Grody and Desnick, 2001; Grody et al., 2001; Vintzileos et al., 1998). This recommendation was based on cost analysis and cost–benefit evaluations. Because such clinical practice is already considered to be the standard of care in the USA, the cost of screening was not included in the model for this study.

Prenatal screening–elective termination is considered to be a cost–effective strategy to prevent the birth of children with CF (Asch et al., 1998; Murray and Cuckle, 2001; Nielsen and Gyrd-Hansen, 2002; Vintzileos et al., 1998). From a purely economic perspective, prenatal testing and elective termination is preferable to IVF–PGD. If patients have no reservations about elective termination, that is certainly a viable option. When a +/+ CF couple opting for natural conception does not want to have a child affected with CF, their best option is to perform prenatal testing with the knowledge that they may face the decision to terminate the 25% of the pregnancies where the fetus is affected with CF. However, prenatal screening–elective termination has not been particularly successful in preventing the birth of children with CF because many patients (perhaps up to 70%), including parents of children suffering from CF, elect not to perform prenatal testing and/or not to terminate an affected pregnancy because of ethical and personal considerations (Chamayou1 et al., 1998; Henneman et al., 2001; Pergament, 1991). Some couples may object to any intervention in the natural conception process. One of the most important questions is how many couples would opt to choose PGD over prenatal diagnosis (PND). 74% of these couples preferred testing with PGD. When PGD could be performed without any significant delay, 80% preferred PGD over PND (Musters et al., in press). Thus, even assuming about 50% reduction in the total number of +/+ CF couples that will elect to undergo IVF–PGD treatment (2000 instead of 4000) will still keep the positive cost analysis. There will be no delay in reaching the break-even point and the net saving is $14.2 billion. In addition, once an IVF–PGD programme is initiated, several hundreds of abortions and their potential complications would be prevented each year. Avoiding the emotional stress and pain by preventing the birth of a child with CF is a major benefit of the IVF–PGD option. Over the 37-year program, thousands of pregnancy terminations would be prevented. By using long-term IVF–PGD programs, a total of 33,444 new CF births would have been avoided. Thus, 618,714 cumulative years of patients suffering because of CF could have been prevented after 37 years (**Table 5**).

The present model benchmarks the costs of IVF–PGD against saved CF treatment costs. Indirect costs, including loss of productivity for CF patients and their caregivers, quality of life and psychological issues as well as the emotional distress, have not been included even though they are quite significant. Having a healthy baby instead of one with CF means that in addition to avoiding lifetime direct medical treatment expenses, the indirect costs and production value over a lifetime are gained. These additional benefits have not been built into the current model but are significant and should be considered when estimating the net value of IVF–PGD. While using the Markov model for cost–benefit analysis with direct costs and benefits, other researchers reached similar conclusions that PGD provides substantial net benefits relative to natural conception, regardless of maternal age (presented at the ASRM 2007; P-396) (Davis et al., 2007).

About 10–15% of couples have infertility. A slightly fairer cost comparison might be made by removing the cost of IVF for couples that would seek IVF for conception because of their infertility and not because of PGD. Again, for simplicity, all patients were included as having IVF treatment just because of the PGD.

The present study includes 104 IVF–PGD cycles. This is the largest series of +/+ CF couples published in the USA and probably the world's largest series from one PGD centre. For comparison, the European Society of Human Reproduction and Embryology PGD consortium has recently summarized the experience of 16–50 centres of 335 cycles reaching PGD for CF performed in 1999–2003 (Sermon et al., 2007). The 35.6% take-home baby rate for women up to age 42 years for IVF–PGD presented here compares very favourably with contemporary IVF success rates as compiled by the US Centers for Disease Control and Prevention. A recent summary of patients less than 35 years old who underwent IVF–PGD for single-gene disorders such as CF, during 2002–2006 at IHR and RGI, yielded a take-home

baby rate of 49% per cycle (Tur-Kaspa et al., 2007). At this success rate, the cost per non-affected delivery decreases by about 27% (to $41,937) and significantly increasing the net savings of the program.

A presumably fertile patient is subjected to IVF when IVF–PGD is used to select embryos with specific genetic conditions. The question then becomes whether patients and babies born are subjected to significant risks. The current consensus is that the risk of IVF is minimal, except for that associated with establishing pregnancies with multiple fetuses (ACOG, 2005). With IVF–PGD, fertilization is typically achieved by ICSI to minimize the risk of contaminating the tested embryonic DNA with that of spermatozoa that may be attached to the surface of the oocyte. ICSI is currently thought to be associated with a slight increase in the incidence of genetic abnormalities (Hansen et al., 2002). However, it is not clear whether the increased risk associated with ICSI is due to the procedure itself or results because the procedure is typically used for the treatment of patients with male infertility (Verpoest and Tournaye, 2006). When IVF–PGD cycles are performed at experienced centres, ICSI, as well as multiple micromanipulations for PGD, do not significantly compromise embryonic development *in vitro* (Cieslak-Janzen et al., 2006). Children born after PGD show no increased risk for minor or major malformation compared with IVF/ICSI cycles with no PGD (Banerjee et al., 2008; Sermon et al., 2007; Strom et al., 2000; Tur-Kaspa et al., 2005). Furthermore, PGD families showed no evidence of excess stress in their relationship with their child (Banerjee et al., 2008).

PGD can be performed for any identified gene mutation. Most IVF–PGD cycles are currently performed for the most frequent mutations such as CF, β-thalassaemia, spinal muscular atrophy, sickle-cell anaemia, myotonic dystrophy, Huntington disease, Marfan syndrome, Charcot–Marie–Tooth disease, achondroplasia, fragile X syndrome, Duchenne muscular dystrophy and haemophilia (Sermon et al., 2007). The list of diseases that can be diagnosed by PGD is being updated frequently with newly identified disease-associated gene mutation (http://reproductivegenetics.com/single_gene.html#singlegene1).

At present, no cure for CF has been identified. In the future, if a new, inexpensive and novel treatment that overcomes the debilitating effects of CF becomes available, that might significantly affect the results of similar cost–benefit studies.

In summary, offering IVF–PGD to all CF carrier couples who wish to conceive without facing the dilemma of possible pregnancy termination or raising a sick child is highly cost effective and will save billions of dollars in direct health expenditures. Delivering a healthy baby instead of one affected with CF means avoiding not only direct medical treatment expenses, but also avoiding the significant loss of productivity and quality of life for CF patients and their caregivers over a lifetime. The potential implications of implementing IVF–PGD for all carriers are remarkable not only from an economic perspective but also from a moral, ethical and personal perspective for families that carry a genetic disorder. Using large-scale national IVF–PGD as a novel preventive medicine strategy to avert the birth of persons with life-shortening and/or severely debilitating genetic disorders has potential profound implications in modern healthcare. This study recommends a national IVF–PGD program to be based at six established IVF centres, one in each US region, along with one to three established central PGD laboratories. While these centres will need to accommodate the increased demand, no new facilities are required. Since calculations were based on number of cycles performed, no increase in operational cost is expected.

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