An evidence-based policy for the provision of subsidised fertility treatment in California: Integration of array comparative genomic hybridisation with IVF and mandatory single embryo transfer to lower multiple gestation and preterm birth rates

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An evidence-based policy for the provision of subsidised fertility treatment in California: Integration of array comparative genomic hybridisation with IVF and mandatory single embryo transfer to lower multiple gestation and preterm birth rates

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AUTHOR'S DECLARATION

I declare that the present work was carried out in accordance with the Guidelines & Regulations as established by the University of Westminster.

This thesis represents my own work, and where any material may be construed as the work of others, it is fully cited and referenced and/or with appropriate acknowledgement given.

Signed: Eric Scott Sills London, 15th May 2013

Table of Contents

List of Figures

List of Tables

Abbreviations

aCGH	array comparative genomic hybridisation
DNA	deoxyribonucleic acid
EHB	essential health benefit
ET	embryo transfer
GA	gestational age (at birth)
HHS	U.S. Dept. of Health & Human Services
IOM	U.S. Institute of Medicine (National Academy of Sciences)
IVF	*in vitro* fertilisation
LBW	low birthweight (infant)
MET	multiple embryo transfer
NICU	neonatal intensive care unit
PPACA	Patient Protection & Affordable Care Act, 2010 ("Obamacare")
PT	preterm (delivery)
SSC	saline-sodium citrate (buffer)
SET	single embryo transfer
SNP	single nucleotide polymorphism

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Abstract

Common to other practice settings, standard *in vitro* fertilisation (IVF) in California strongly skews the multiple gestation/preterm birth rate upward to approximately 50% of all deliveries, while unassisted conceptions yield this outcome in only 3% of births. Preterm/multiple gestation babies from IVF are “super-utilisers” and consume a disproportionate share of healthcare resources, particularly during the first year of life. However, early experience with molecular cytogenetic techniques has shown that single embryo transfer (SET) with IVF can now lift pregnancy rates to an acceptable level while not altering the normal multiple gestation rate. This approach would effectively solve the preterm and multiple gestation problem historically associated with IVF.

Building on the author’s previous research in medically assisted reproduction, the current proposal describes a new public health policy to incentivise SET by modifying the California Insurance Code (benchmark health plan), when it may next be revised in 2015. The proposal would partially cover IVF costs for qualified California residents with the proviso that only one embryo is transferred per procedure after comprehensive chromosomal screening of embryos with array comparative genomic hybridisation (aCGH). This investigation considers the interconnected problems of preterm birth and multiple gestation in a demographic context, showing that although the contribution made by conventional IVF to these adverse outcomes in California is numerically minor, substantial costs can still be recovered by redirecting expenditures away from high-risk IVF deliveries when the increased multiple gestation/preterm birth rate from standard IVF is corrected.

This analysis is the first to examine costs calculated for all delivery types in California as a function of antecedent IVF treatment vs. unassisted conception, based on 2009 birth records, and apply this to a new model of comprehensive embryo testing and mandatory SET. These data reveal that even if partially subsidised IVF with aCGH and SET were provided for every California IVF cycle initiated in 2009 (*n*=18,405), the state would still realise a net surplus of at least $20M per year by stabilising the IVF multiple birth rate at ~3.2%. Thus, California can avoid up to 4,810 iatrogenic preterm/multiple gestation births by shifting the prevailing approach to IVF away from multiple embryo transfers. The proposal is net revenue positive for California because although IVF with aCGH and SET is expensive, the price to obtain this technology is always lower than the cost for one high-risk preterm/multiple birth. While a compelling primary interest exists to lower the multiple birth rate with IVF, this proposal also yields a socially valuable secondary public health benefit by improving general access to this advanced reproductive treatment for all Californians.

Aims

To optimise effectiveness in public health spending in California by lowering the proportion of multiple gestation and preterm births from *in vitro* fertilisation (IVF) in the state, and to equalise access to IVF for all Californians.

Objectives

The following objectives will be informed by evidence primarily sourced from the author's published works and, where appropriate, corroborated with the work of others:

1. To review the process of IVF and to review customary funding structures for IVF in California with an emphasis on how this might be affected by recent changes in health care funding,

2. To calculate IVF's contribution to multiple births and preterm delivery in California, and measure the economic impact of these outcomes,

3. To establish how single embryo transfer (SET) attenuates the problem of multiple births and preterm delivery associated with IVF, and

4. To forecast the recovery of health spend in the context of SET if IVF were partially offset in California with state support.

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1. Introduction & Background

Public interest in American healthcare reform was crystallised in the recent enactment of the Patient Protection & Affordable Care Act, 2010 (also known as PPACA or "Obamacare"). While offering essential healthcare coverage for most Americans is the chief aim of this landmark legislation, PPACA also provides an opportunity to resolve two longstanding and closely related health policy challenges affecting a special population: to reverse the rising rates of higher-order multiple gestation/preterm births, and to improve general access to *in vitro* fertilisation (IVF). These two objectives seem to reflect a conflicted, intractable healthcare dilemma, because making IVF (and its customary multiple embryo transfers) more available can be reasonably expected to exacerbate multiple gestation and preterm delivery rates.

Delivery of a healthy singleton live birth is the ideal outcome for all medical infertility treatment. During *in vitro* fertilisation (IVF), multiple embryos are typically transferred because any individual embryo may contain serious chromosomal error, which can result in implantation failure or spontaneous abortion (Sills *et al.,* 2012b). Strategies to improve embryo implantation have included sequential (compound) transfer, whereby embryos are transferred on more than one day (Hayrinen *et al.,* 2012), although this is not routine practice. For each IVF patient who undergoes transfer of more than one embryo at a time—which is the great majority of cases—her treatment culminates with the hope that at least one embryo will successfully implant and bring a healthy pregnancy. Generally, IVF embryos are chosen for transfer based on their appearance as determined by microscopic examination. Selecting embryos for transfer based on

morphologic criteria alone is imprecise, because there is essentially no correlation between the embryo's appearance (morphology during the first several days after fertilisation) and its genomic status (Alfarawati *et al.*, 2011). For example, a significant proportion of aneuploid embryos will demonstrate the highest morphologic score, while some euploid embryos will be of inferior morphology (Alfarawati *et al.*, 2011). Even the most junior embryologist quickly notes how the transfer of poor quality embryos can result in healthy IVF babies, yet normal looking embryos fail to implant after transfer (Sills *et al.*, 2012b). Recently, the continuous morphological evaluation by uninterrupted video monitoring of embryos during *in vitro* culture has been proposed as a way to address some of the shortcomings of standard embryo scoring systems (Campbell *et al.*, 2013). While this approach does offer a fuller picture of early embryo morphokinetics, chromosomal competency of embryos cannot be ascertained by this method. Thus, visually picking the "right" embryo for transfer in IVF remains a high stakes challenge, since less than 15% of embryos may actually implant and grow into healthy infants (U.S. Centers for Disease Control and Prevention, 2008).

Against this background, any expectation that standard microscopic examination of embryos could secure any meaningful surveillance of genetic error before transfer is unrealistic; the traditional practice to select by morphology helps explain why the efficiency of single embryo transfer protocols has remained so low. Since many IVF patients will accept a higher twinning risk in exchange for a meaningful reduction in overall treatment failure (Pinborg *et al.*, 2003; Højgaard *et al.*, 2007), multiple embryo transfer has emerged as the mainstream clinical response to this challenge (Sills *et al.*,

2009d). Following this approach, some IVF patients may conclude their treatment with a singleton gestation despite multiple embryos being transferred. Yet, the IVF patient who undergoes transfer of multiple embryos must be prepared for one of two very unsettling outcomes. Either she will not conceive at all, or a multiple gestation will result—the degree of multiple gestation and preterm birth being determined by how many embryos were transferred (Kern, 2009; Sills *et al.*, 2012b). This latter circumstance poses significant risk both for mother and offspring, including increased incidence of preeclampsia, postpartum hemorrhage, hysterectomy and gestational diabetes (Walker *et al.*, 2004), as well as greater risk of preterm delivery, low birthweight infants, cerebral palsy and congenital malformations (Bergh *et al.*, 1999; Sills & Palermo, 2002a; Stromberg *et al.*, 2002; Pinborg et al., 2003).

The health benefits of a single embryo transfer approach were dramatically revealed by a Danish study of IVF outcomes, where cerebral palsy incidence was measured among 1,042 IVF singletons born after only one embryo was transferred. Just one of those babies received a cerebral palsy diagnosis, compared with 21 cerebral palsy cases among IVF singletons born after two or more embryo transfers (Hvidtjørn *et al.*, 2010). In Canada, efforts to mandate single embryo transfer gained momentum when this change in IVF practice was shown to prevent infant deaths and reduce serious complications associated with multiple gestations (Voelker, 2011). Such research illustrates how IVF babies comprise an important class of healthcare 'super-utilisers' (Koivurova *et al.*, 2007). Indeed, a recent study of NICU admissions at one hospital found 75 of 82 infants to be twins or triplets whose mothers relied on IVF to become pregnant. Among those 75

babies there were six deaths, and five more developed severe brain hemorrhage (Voelker, 2011). Such statistics for multiple gestation and preterm birth trace a similar arc as closely interrelated consequences of increased IVF use. Notwithstanding the devastating emotional impact these tragic outcomes have on patients and their families, the fiscal burden on hospital resources is enormous.

Clearly, any public health effort to tackle the alarming costs of multiple gestation and preterm birth will have diminished effectiveness without recognising IVF's contribution to the problem. The most obvious remedy for multiple gestation in the setting of IVF is single embryo transfer, but several factors including an unfavorable reimbursement system have hindered the uptake of this approach (van Peperstraten *et al.,* 2008).

This original research places one of these new technologies, array comparative genomic hybridisation (aCGH), at the center of a treatment initiative designed to address the intertwined healthcare issues of excessive rates of multiple gestation and preterm birth from IVF, while at the same time improving access to this treatment recognised as highly effective in the struggle against infertility. This proposal entails embryo biopsy performed on day five and SET the next day, rather than requiring an embryo transfer be undertaken later in a subsequent frozen transfer cycle. Array CGH has been refined (Sills *et al.*, 2012b) and awaits recognition by government and insurance as a way to incentivise single fresh embryo transfer among IVF patients.

2. Limitations of Conventional IVF

For IVF patients, becoming a parent hinges on the successful completion of a medical odyssey comprising a fretful maze of tests and expensive procedures (Sills *et al.*, 2010c). The complexity and high cost of IVF relates to the interlock of ovarian screening, clinical management during oocyte development, laboratory incubation/culture, and embryo transfer. At present, treatment effectiveness is low especially for older IVF patients with success rates adversely impacted by ovarian ageing (Sills *et al.*, 2009e). Transferring three or more embryos at a time is a common way to address the problem of poor embryo implantation in such cases, although oocyte donation may also be considered (Sills *et al.*, 2010a,b,c).

In general, procedures or treatments which include the laboratory (*in vitro*) manipulation of human spermatozoa, oocytes, or embryos for the purpose of achieving pregnancy are classified as advanced reproductive techniques (Zegers-Hochschild *et al.*, 2009). A typical IVF cycle consists of ovulation induction with injectable gonadotropins to recruit multiple mature oocytes, surgical removal of the mature eggs under anaesthesia, fertilisation of eggs under controlled laboratory conditions to build embryos (Sills & Palermo, 2010), and the transfer of embryos to the uterine interior. Non-transferred (surplus) embryos which remain after fresh transfer may be cryopreserved, with subsequent thaw and transfer to the patient at some later date (Sills *et al.*, 2008; Sills & Murphy, 2009; Sills *et al.*, 2009b). For all patients seeking this elective fertility treatment, only about 20% of IVF attempts (either fresh or frozen) will result in a livebirth (Chambers *et al.*, 2012).

Not every patient who wishes to do IVF will be medically suitable for this treatment, so pre-enrolment testing is essential. This is because fertility potential first declines after age 30 and moves downward rapidly thereafter, essentially reaching zero by the mid-40s (Sills *et al.*, 2009a). The concept of ovarian reserve describes the natural oocyte endowment and is closely associated with female age, which is the single most important factor influencing reproductive outcome. Conceptions at advanced age are exceedingly rare even with IVF, unless oocytes obtained from a younger donor are utilised (Sills *et al.*, 2010b). How best to measure ovarian reserve remains an area of active research (Sills *et al.*, 2009a). Passive assessments of ovarian reserve include measurement of serum follicle stimulating hormone (FSH), oestradiol (E_2), anti-Müllerian hormone (Sills *et al.*, 2011), and inhibin-B. Ultrasound determination of antral follicle count (AFC), ovarian vascularity and ovarian volume may also have a role. The clomiphene citrate challenge test (CCCT), exogenous FSH ovarian reserve test (EFORT), and GnRH-agonist stimulation test (GAST) are provocative methods which may be helpful in assessing ovarian reserve (Sills *et al.*, 2009a). Importantly, an IVF patient's prior response to gonadotropins also provides highly valuable information about ovarian function (Sills *et al.*, 1998).

These tests are complemented by the male factor evaluation, also a critical part of basic fertility screening. A standard semen analysis is essential to a thorough reproductive work-up. Recently, other more sophisticated andrology testing has been described to supplement the basic semen analysis before commencing IVF, including assessment of nuclear (sperm) chromatin fragmentation (Sills *et al.*, 2004; Bungum *et al.*, 2012). As

with the female, a general endocrine evaluation may also be indicated for the male since hormonal disruption in the man can impair semen parameters (Saie & Sills, 2005).

Fertility patients not conceiving after multiple IVF attempts typically face a difficult prognosis. The impact of increased refractoriness to IVF on reproductive outcome following transfer of blastocysts (day 5 embryos) has been studied among patients with a history of repetitive failed day three embryo transfers (Walsh *et al.*, 2009b). There is no consensus guiding medical decisions after such multiple IVF failures (Tan *et al.*, 2005), but maternal endocrine, anatomic, immunologic, infectious, and genetic parameters are typically investigated (Christiansen *et al.*, 2006). In circumstances where immunological pathology is suspected as a cause for recurrent miscarriage, corrective therapies can result in pregnancy and healthy delivery (Sills *et al.*, 2004a; Sills *et al.*, 2009c). Yet, because the incidence of chromosomal abnormality is higher in embryos from patients experiencing multiple IVF failures (Voullaire *et al.*, 2007), much attention has been focused on embryo genetics as the most important reason for poor IVF outcomes. Blastocyst nidation is impaired in the setting of embryo aneuploidy, making this the key step in overall reproductive outcome (Boomsma & Macklon, 2008; Walsh *et al.*, 2009b). For example, when pre-implantation genetic diagnosis (PGD) data are studied from embryos obtained from patients who have experienced multiple IVF failures, aneuploidy is more often observed in the cycle following the initial failure (Pagidas *et al.*, 2008). Thus, an impaired capacity to produce reproductively competent embryos is the critical associative factor among patients with recurrent IVF failure (Farhi *et al.*, 2008).

3. Array CGH—Technique & Logistics

Array comparative genomic hybridization (aCGH) accomplishes selection of euploid embryos for fresh transfer first by whole genome amplification of each embryo, performed on-site at the IVF laboratory using the SurePlex DNA amplification system (BlueGnome Ltd; Cambridge, UK) in accordance with manufacturer's guidelines (Alfarawati *et al.*, 2011; Yang *et al.*, 2011).

In brief, trophectoderm biopsy samples (1-2 cells) and control DNA (8 μl each) are labeled with Cy3 and Cy5 fluorophores (BlueGnome Ltd; Cambridge, UK). Labeling time is typically three hours with DNA resuspended in dexsulphate hybridization buffer, before being placed on an array slide for hybridisation. After saline sodium citrate (SSC)/0.05% Tween-20 irrigation at room temperature, an additional ten minute wash in SSC is completed at room temperature. Slides are next washed in SSC for five minutes at 60°C and again for one minute at room temperature. A vacuum centrifuge is used to dry microarray slides with subsequent laser scanning at wavelength 10 μm (Agilent Technologies; Santa Clara, USA).

Microarray data are analyzed with BlueFuse software (BlueGnome, Cambridge, UK) to determine chromatin loss or gain across all 24 chromosomes. In general, aberrations are considered non-artifact if 15 or more probes deviated from normal limits as defined by the 24Sure platform. The published accuracy rate for this methodology when applied to trophectoderm cells is 95% (Alfarawati *et al.*, 2011; Sills et al., 2012b). Embryo ploidy

data is usually ready early enough to allow fresh transfer of a single embryo on day six (morning).

When multiple euploid blastocysts are available, the euploid blastocyst with the best morphology would be chosen for fresh transfer. Surplus euploid blastocysts are vitrified for future use (Liu *et al.,* 2012a). As shown in Figure 1, aCGH represents an additional crucial step in the IVF treatment process, following fertilisation and biopsy, at a time when morphology alone would typically be used exclusively to select embryos for transfer. Since aCGH consumes only about 12 hours of laboratory time after embryo biopsy, this eliminates the need to freeze all IVF embryos after biopsy with shipment of the biopsy samples for off-site testing. Fresh (single) embryo transfer can be performed on day six, thus obviating the need for additional medication (and at least one month delay in treatment) associated with subsequent frozen/thaw embryo transfer (see Figure 2).

There is some controversy regarding the ideal developmental stage when embryo biopsy for aCGH should be performed (Yang *et al.,* 2011). The reduced cellular mosaicism at day five (compared to day three) has led some centres to prefer biopsy at the blastocyst (d5) stage. When combined with trophectoderm biopsy and blastocyst vitrification, SNP microarray has resulted in high implantation rate and low miscarriage rates for some poor prognosis IVF patients (Schoolcraft *et al.,* 2010). Prior to May 2012, there was no published experience with aCGH in selecting a euploid blastocyst for single fresh transfer in the absence of any known parental chromosomal diagnosis.

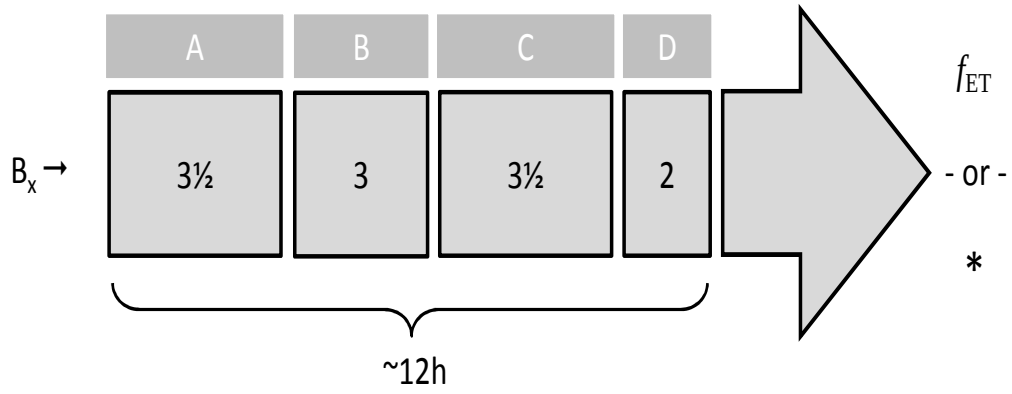

Figure 1. Integration of array comparative genomic hybridisation (aCGH) with the in vitro fertilisation sequence. This schematic depicts aCGH components and time requirements (in hours) for each: A) sample preparation and genomic amplification, B) labeling, C) hybridisation, and D) scanning/reporting. Biopsy of embryonic trophectoderm at day five (blastocyst stage) is shown at Bx, and fresh single embryo transfer on day six corresponds to f_{ET}(d6). This protocol enables comprehensive chromosomal screening within 12 hours of biopsy, thus obviating the need for empiric cryopreservation of all embryos while off-site results are returned. Surplus euploid embryos remaining after fresh transfer may be cryopreserved (✱) for future use.

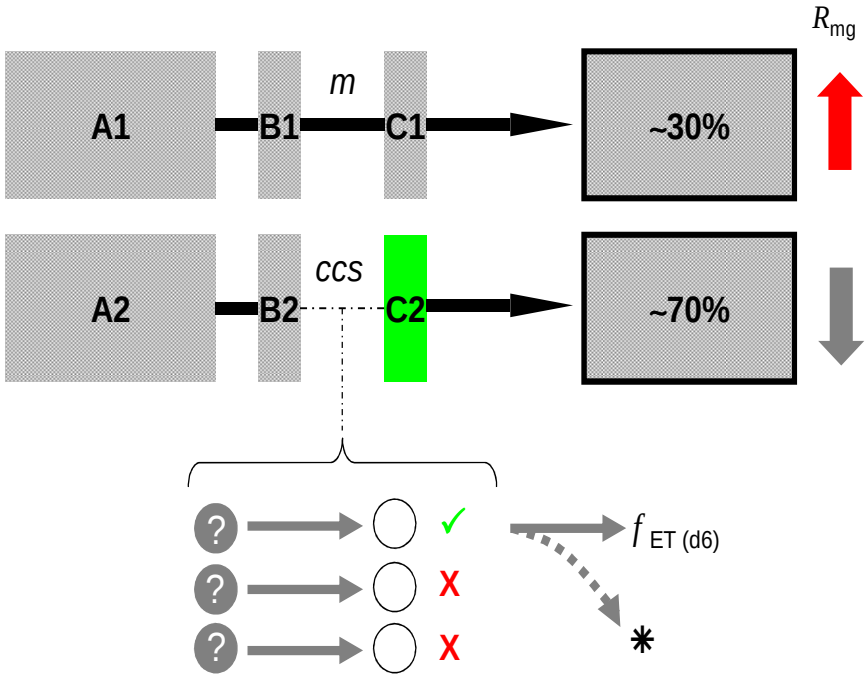

Figure 2. Schematic of conventional IVF (above) and IVF with aCGH (below), indicating follicular recruitment/ovulation induction (A1,A2) and oocyte retrieval/ICSI (B1,B2) steps in each treatment sequence. Comprehensive chromosomal screening (ccs) occurs instead of traditional morphological assessment of embryos (m), identifying any aneuploid embryos (red x). This permits selection of a single euploid embryo (green check) for fresh transfer (C2) or cryopreservation (✱). Pregnancy rates nearing 70% have been reported after fresh transfer of one euploid embryo using this technique ($f_{ET(d6)}$) , with significant reduction in multiple gestation rate (R_{mg}).

Encouraging data now show a way forward to augment IVF with aCGH, and to do so in a highly cost effective manner (Sills *et al.*, 2012b).

A recent investigation (Yang *et al.*, 2012) enrolled IVF patients willing to undergo fresh single blastocyst transfer with embryos randomised either to assessment by morphology alone, or by morphology plus aCGH. Researchers analysed 425 blastocysts via aCGH, and aneuploidy was present in 44.9%. These normal appearing embryos would have been considered suitable for transfer based on morphology, but chromosomal error

would have rendered them reproductively incompetent. As reported by Yang and colleagues (2012), the age-matched patient control group contributed 389 blastocysts which were assessed traditionally, by microscope only (no aCGH). This new approach substantially improved IVF efficiency, with clinical pregnancy rates increasing by 65% over the observed rate when conventional morphology alone was used to select single embryos for transfer (Yang *et al.*, 2012).

Of note, there were no twin or triplet pregnancies in either group. The clinical pregnancy rate was significantly higher in the morphology plus aCGH group compared to the morphology-only group (70.9 and 45.8%, respectively; p=0.017). The publication appearing in the journal *Molecular Cytogenetics* remains among its most highly-accessed papers, and was the first to describe integrating embryo screening via aCGH with standard IVF and single blastocyst transfer (Yang *et al.*, 2012). Such synergy between advances in genetics and embryology seems positioned to usher in a new era in the treatment of infertility (Fragouli & Wells, 2012; Sills *et al.*, 2012b), although thus far there has been little awareness of the potential economic impact of these studies or how they might shape public health policy.

Although the use of highly accurate molecular tests to identify genetic conditions has been established for some years (Sills *et al.*, 2002 & 2007), expenses can vary depending on which test is used. The additional cost associated with including aCGH during IVF to assess multiple embryos in a cohort has been calculated at approximately $3000 (Yang *et al.*, 2012; Sills *et al.*, 2012b). It should be noted that current testing modalities permit

several embryos to be tested at the same time, depending on which aCGH platform is used. In contrast, average NICU costs typically exceed $3,500 per infant per day, and it is not uncommon for this figure to top $1M for a prolonged stay (Muraskas & Parsi, 2008). California can be the first state to implement a health benefit programme that recognises the social and economic value of offering a regulated, public IVF plan as a way to manage these “first year of life” healthcare costs. Yet, to do so will require acknowledging the key role of aCGH in potentiating single embryo transfer in IVF.

4.1. How Many Embryos for Transfer?—Current Regulations (International)

Except for Sweden and Belgium (De Neubourg *et al.,* 2006; Karlström & Bergh, 2007), all other jurisdictions permit the number of embryos for transfer to be whatever the IVF doctor and patient want, so the clinician's role in this process is vital (van Peperstraten *et al.*, 2008). While some may favour the unregulated flexibility where the number of transferred embryo is not legally limited (Gleicher, 2011), one noteworthy case in California focused negative attention on the undesirable outcomes associated with a very high number of embryos transferred and the associated preterm delivery of octuplets (Kern, 2009; Rosenthal, 2011). Resistance to regulating number of transferred embryos derives from principles of procreative liberty, patient and professional autonomy, and free-market economics (Gleicher, 2011). In contrast, others have countered that IVF physicians must fulfill their professional fiduciary responsibility to balance nonmaleficence and proper utilisation of limited health care resources with patient requests to transfer multiple embryos (Van Voorhis & Ryan, 2010).

These two viewpoints represent interesting arguments for "self-pay" medical consumers in the United States. For IVF patients, the goal is simply to get pregnant quickly, thus the "freedom of choice" (unregulated) model has strong appeal. Indeed, when elective medical choices are influenced by free-market forces, the consumer's interest in single embryo transfer can be very low because this approach is associated with reduced per-cycle pregnancy rate (Le Lannou *et al.*, 2006) and delayed "time-to-pregnancy" (Lukassen *et al.*, 2005). When elective SET is undertaken on the basis of conventional morphology assessment alone, this consistently gives reduced delivery rates compared to

dual embryo transfer, a result demonstrated in every randomised clinical trial published to date (Forman *et al.*, 2012). However, assuming the success rate with SET could be increased to approach that of double embryo transfer, then patient acceptance of single embryo transfer would surely improve (Leese & Denton, 2010).

Even where rules governing embryo transfer are in effect, there has never been specific regulation addressing how the single embryo must be selected. Thus far, legislation has been silent on this matter perhaps because it represents a contentious, evolving area of reproductive genetics: there is no scientific consensus yet on the optimal method to determine the competency of the embryonic genome during IVF. Single nucleotide polymorphism (SNP) array and array CGH (aCGH) have both been validated as accurate methods to achieve comprehensive chromosome screening when embryo biopsy is performed on d3 for fresh transfer on d5 (Hellani *et al.,* 2008; Fishel *et al.,* 2010; Fioretino *et al.,* 2011; Gutierrez-Mateo *et al.*, 2011; Handyside, 2011).

As California contemplates its own programme for subsidised IVF coverage where the number of transferred embryos is limited to one, looking to Belgium perhaps best illustrates how this could be implemented. A law regulating the number of transferred embryos there became effective in July 2003 (Salame *et al.,* 2011). Belgian IVF regulations actually stipulate a strong preference for single embryo transfer, but provisions for exceptions do exist. Specifically, for patients age less than 35 years undergoing fresh non-donor transfers (*i.e.*, not using cryopreserved embryos or oocyte donation), the first attempt is limited to one embryo for transfer. After the second IVF

attempt, a two embryo transfer is the maximum allowed. When the patient is age 35-40, a two embryo transfer is the maximum permitted for first and second IVF attempt, but three embryos may be transferred on the third cycle. As patient age approaches 43, there is no limit on the number of embryos transferred (Salame *et al.,* 2011). Thus, single embryo transfer has been mandatory for IVF patients up to age 35 years in Belgium for nearly ten years; contrasting multiple gestation rates in this group before and after implementation of this policy is highly relevant to the current proposal. Belgium's restriction in the number of embryos for transfer has led to a significant reduction of the multiple pregnancy rate, associated with a clinical pregnancy rate of 36.8% overall among IVF patients under age 36 (Salame *et al.,* 2011). This success rate with SET is similar to the clinical pregnancy rate observed in Belgian IVF patients who undergo a two-embryo transfer (37.5%, $p>0.05$), although the observed twinning rate is significantly lower (8.3 vs. 22.4%, $p<0.001$) (Salame *et al.*, 2011).

Of note, Belgian policies on embryo transfer (and ovarian stimulation) have not included any requirement for comprehensive chromosomal screening of embryos before transfer (the law was developed during a time when aCGH was not yet widely used in reproductive medicine), which could explain why overall pregnancy rates are lower than those reported when aCGH is used with IVF (Liu *et al.*, 2012a,b; Sills *et al.,* 2012b; Yang *et al.*, 2012). Nevertheless, savings realised by the Government of Belgium from reductions in health spend associated with neonatal intensive care (and pharmacy savings) now enables the Belgian national insurance system to subsidise up to six IVF cycles for eligible patients up to age 43 (Salame *et al.*, 2011).

Important improvements in comprehensive chromosomal screening of embryos have been reported in the decade since Belgium's law was enacted. Experience with aCGH and IVF now shows that clinical pregnancy rates from IVF can nearly double even if only one (euploid) embryo is transferred (Liu *et al.*, 2012a; Yang *et al.*, 2012). This means that almost no IVF patient would require six fresh cycles, since each attempt can yield a pregnancy rate of about 70% (Liu *et al.*, 2012a; Sills *et al.*, 2012b; Yang *et al.*, 2012). Because IVF is so closely connected to the problem of multiple births, and considering the avoidance of iatrogenic twin, triplet and higher-order gestations would result in significant savings in health spending (Lukassen *et al.*, 2004; Salame *et al.*, 2011), a critical appraisal of single embryo transfer following IVF and aCGH is now appropriate.

Does government have an interest in the provision of this elective medical service? Connolly and co-workers (2009) developed a model to quantify the lifetime net tax position for the child (either naturally conceived, or born after IVF), and found a positive revenue gain for the government. Indeed, the only difference between the two scenarios (unassisted pregnancy *vs.* IVF) was confined to the additional cost of IVF required for conception. Using this formula, it was determined that an initial investment of £12,931 for IVF would yield an 8.5-fold return to the state over the child's taxpaying lifetime (Connolly *et al.*, 2009).

Before any new public health initiative may be considered, it is essential to anticipate costs and yields. When IVF was studied as a benefit under the remit of the National

Health Service, investigators from the United Kingdom (Connolly *et al.*, 2009) described a health investment model embracing multiple factors. The researchers estimated discounted future net tax revenue to the government, based on average "investment cost" for IVF needed to add one extra taxpayer to the national population by achieving a singleton live birth. This analysis was based on the formula modified from Cardarelli and colleagues (2000):

$$C_L\,(t) = T(g) - E\,(t) - H\,(t) - C\,(t) - P_S\,(t)$$

where $T(g)$ is gross tax revenue received, $E(t)$ and $H(t)$ correspond to the state's education and healthcare expenditure, and $C(t)$ represents child tax credits. Roles of government pension costs and privately-funded retirement pension are considered jointly, as taxation returns from private pension (from which the state receives additional revenue by pension tax) are factored as $Ps(t)$. Accordingly, the net lifetime tax contribution to government may be estimated by $C_L(t)$.

Yet revenue returns predicted by the Cardarelli formula have greatest traction when every IVF attempt is a success, and each pregnancy gives a singleton livebirth. Unfortunately, current IVF practice cannot realistically deliver this level of clinical service (Sills *et al.*, 2009a). With an IVF treatment cost indexed at £12,931, and considering standard IVF in the United Kingdom typically costs about £3,500 per treatment (Sample, 2011) the formula clearly acknowledges the need for multiple attempts. Nevertheless, the predicted return could be substantially enhanced if IVF were

refined to produce higher pregnancy rates with a multiple gestation rate identical to the background population level.

The impact of IVF on national birth rate and multiple gestation trends has been reported from other countries (Sills *et al.*, 2010d), and California's savings from avoiding IVF multiple gestation/preterm births from IVF may also be calculated. These projections are extrapolated from earlier work (see Table 1) where one vs. two embryo transfer costs were compared (Wølner-Hanssen & Rydhstroem, 1998).

Table 1. Selected women's healthcare costs (historical) as a function of number of embryos transferred during IVF, per patient.

	Embryos transferred (*n*)		
Cost element	One	Two	Δ
Sick leave	1830	4122	2292
In-patient care	866	2785	1919
Obstetrical care (delivery)	2760	4970	2210
Neonatal care	1988	13279	11291
Disability payments	3280	18130	14850
Total	10724	43286	32562

Notes: All costs reported in 1995 Swedish Krone. Table adapted from Wølner-Hanssen & Rydhstroem (1998).

Additionally, where there is increased risk for offspring affected by chromosomal conditions (*i.e.*, advanced maternal age), aCGH could provide participating patients with information on embryo ploidy status before transfer (Hellani *et al.*, 2008). To be sure, society already carries much of the economic burden from complications associated with

multiple gestation, so governments have a compelling regulatory interest in how IVF is provided. The problem has been that, until now, there was no effective technology available to use with IVF to address these goals. Now that aCGH has been shown to fill this role and safely lift singleton pregnancy rates from IVF, continued provision of traditional IVF with multiple embryo transfers seems unnecessary. As shown in the next section, implementation of the current proposal in California would entail the state offsetting relatively small initial costs in the short term, with an expectation that substantial savings from reductions in "first year of life" healthcare spending are appreciated from dramatically lowered multiple gestation rates (Wølner-Hanssen & Rydhstroem, 1998).

4.2. How Many Embryos for Transfer—Proposed Regulations (California)

Interest in medical fertility treatments in general, and IVF in particular, among medical consumers in California remains strong. Since the first tabulation of national IVF data in 1996, the number of pregnancies conceived and infants delivered in the United States with the assistance of IVF has risen nearly threefold (Sunderam *et al.*, 2012)—a growth rate to which California has made substantial contributions. Sixty one IVF clinics operate in California alone, more than in any other U.S. state. In 2009, California residents initiated the highest total number of IVF cycles of any U.S. state.

The economic impact of IVF with regards to multiple gestation and preterm birth is substantial. About half (47%) of all IVF deliveries are multiple gestation, compared to about 3% in the background population (see Table 2a). California and five other states accounted for nearly half (48%) of all American IVF births in 2009, highlighting an unbalanced geographic distribution of IVF utilization in the United States (Sunderam *et al.*, 2012). Interestingly, despite the high absolute number of IVF cycles initiated in California, the state only ranks twelfth in the nation when the number of IVF cycles is measured against the total number of reproductive age women. Most likely, California's lower per capita IVF consumption is due, at least in part, to the state not having a statewide mandate for IVF insurance coverage.

Not having a state insurance mandate for IVF in California is a critical element in this analysis. Unfortunately, IVF coverage is rarely included in private health insurance plans in California and elsewhere in the United States (Sunderam *et al.*, 2012).

Table 2a. Distribution of multiple gestation deliveries after IVF in California (2009).

IVF multiple births		Total multiple births		IVF twins		Total twins		% from IVF	HOM births from IVF		Total HOM births		% from IVF
n	(%)	*n*	(%)	*n*	(%)	*n*	(%)		*n*	(%)	*n*	(%)	
3,566	47.3	16,801	3.2	3290	43.6	16,126	3.1	20.4	276	3.7	675	0.1	40.9

Table 2b. Distribution of California IVF deliveries by gestational age at birth (2009).

<37 weeks GA					<32 weeks GA					32–36 weeks GA				
IVF		All births		% from IVF	IVF		All births		% from IVF	IVF		All births		% from IVF
n	(%)	*n*	(%)		*n*	(%)	*n*	(%)		*n*	(%)	*n*	(%)	
2,405	31.9	53,956	10.2	4.5	413	5.5	7,948	1.5	5.2	1,992	26.4	46,008	8.7	4.3

Notes: IVF = in vitro fertilisation; HOM = higher-order multiple birth (*i.e.*, triplets and higher order gestation); GA = gestational age. Total births tabulated by federal methods differ slightly from State of California vital statistics. Patients without a designated residency status were assigned to California if IVF treatment was performed within the state. This summary includes infants conceived from IVF initiated in 2008 and born in 2009, and infants conceived from IVF performed in 2009 and born in 2009. Source: U.S. CDC/National Center for Health Statistics, in Sunderam *et al*, 2012.

Where state IVF mandates are currently lacking, attempts to minimise out-of-pocket costs have been linked to higher numbers of embryos transferred per patient (Jain *et al.*, 2002). Thus, insurance mandates for IVF appear to be associated with not only improved access to assisted fertility therapy, but also substantially fewer aggressive IVF treatments where lower numbers of embryos are transferred per procedure (Hamilton & McManus, 2012; Jain *et al.*, 2002).

Importantly, 32% of all infants conceived by IVF in 2009 were low birthweight (<2,500 grams), and 33.4% of all IVF babies were delivered preterm (see Table 2b). In California, the contribution of IVF births to all low birthweight deliveries ranges from 6.3% to 6.7% depending on which category of birthweight is considered (see Table 3a). Overall, California's rate of preterm delivery was about 20.5% in 2009, which was somewhat lower than the national average (24.2%, in 2009).

These data highlight the hazards of overestimating the impact of IVF on overall poor delivery outcomes. While transferring more than one embryo in IVF does influence the rate of multiple gestation and preterm delivery (see Table 3b), the prevalence of these poor outcomes cannot be ascribed solely to IVF because this treatment accounts for a relatively small fraction of total births (Sunderam *et al.*, 2012). Of note, a recent study of preterm birth rates in the United States between 1989 and 2004 found that half the increase was of uncertain etiology (Chang *et al.*, 2012).

Table 3a. Distribution of California IVF deliveries by low birthweight category (2009).

<2,500 grams					<1,500 grams					1,500–2,499 grams				
IVF births		All births		% from IVF	IVF births		All births		% from IVF	IVF births		Total births (all)		% from IVF
n	(%)	*n*	(%)		*n*	(%)	*n*	(%)		*n*	(%)	*n*	(%)	
2,373	31.4	35,802	6.8	6.6	384	5.1	6,064	1.2	6.3	1,989	26.4	29,738	5.6	6.7

Table 3b. Comparison of singleton delivery characteristics, IVF and unassisted conceptions in California (2009).

All births (*n)*	Births from IVF (*n)*	IVF contribution (%)	IVF Singleton births		Singleton births (all)		% of IVF singletons to all singleton births
			n	(%)	*n*	(%)	
527,020	7,546	1.4	3,973	52.7	510,219	96.8	0.8

Notes: IVF = in vitro fertilisation. Total births tabulated by federal methods differ slightly from State of California vital statistics. Patients without a designated residency status were assigned to California if IVF treatment was performed within the state. This summary includes infants conceived from IVF initiated in 2008 and born in 2009, and infants conceived from IVF performed in 2009 and born in 2009. Source: U.S. CDC/National Center for Health Statistics, in Sunderam *et al*, 2012.

While the report from the *Born Too Soon Preterm Prevention Analysis Group* did include a recommendation to decrease multiple embryo transfers during IVF as one of five specific initiatives to help resolve the preterm birth challenge (Chang *et al.*, 2012), because the United States has no nationwide database to capture information on gestational age at delivery following IVF, the actual impact of IVF on preterm births cannot be known with precision (Sills & Collins, 2013). For California, general cost parameters for IVF may be extrapolated from the following relations:

$$F(b) \times F(c) = F(t)$$

Where *F(b)* is the total number IVF cycles initiated in California, *F(c)* is the mean estimated cost per IVF cycle (invoiced at $13,000) and *F(t)* represents approximate total health spend on IVF for 2009; and

$$G(b) \times G(c) \begin{cases} G(tm) \\ + \\ G(<37) \end{cases} = G(t)$$

Where *G(b)* is total number of all California births in 2009, *G(c)* is aggregate cost for delivery and infant care [comprised of term birth costs *G(tm)* plus preterm (<37 weeks gestational age) birth costs, *G(<37)*], and *G(t)* is approximate total California health spend on all deliveries for 2009. A variation on this formula can also be used to estimate costs associated with IVF deliveries, although the ratio of term/preterm and multiple gestation births is altered.

Recently published California data give the following information for 2009:

a) Total number of births = 526,744
b) Total number of IVF cycles initiated (completed) = 18,405 (15,953)
c) Births attributed to IVF = 7,546
d) Low birthweight deliveries (total) = 71,604
e) Preterm deliveries (total) = 107,912
f) Low birthweight deliveries from IVF = 4,746
g) Preterm deliveries from IVF = 4,810
h) Estimated term delivery cost = $9,329
i) Estimated preterm delivery cost = $51,600
j) Cost of IVF per cycle (±aCGH) = $10,000 ±3,000

The total number of California births registered in 2009 is reported as 527,020 (federal source) or 526,774 (state source). In this case, the state record was regarded as more accurate (State of California, 2012c) while the remaining entries are federally derived (Sunderam *et al.*, 2012) or from clinic invoices where aCGH is offered on-site with IVF. While the numerical contribution made by IVF deliveries to the overall populations of low birthweight, preterm, and multiple gestation in California is minor, the downstream economic consequence of multiple embryo transfers in IVF is noteworthy.

From a total of 18,405 initiated IVF cycles in California during 2009, about 87% proceeded to embryo transfer. For these patients, the mean number of embryos

transferred during IVF per cycle was never less than two, and this increased with patient age in a manner similar to the national trend as summarised in Table 4.

Table 4. Cycle characteristics and outcomes for U.S. IVF patients, by age (2009)

	Patient age (years)				
	<35	35-37	38-40	41-42	43-44
Total IVF cycles initiated (*n*)	42,384	21,860	22,144	9,845	4,857
Implantations per ET (%)	35.3	25.9	17.2	9.1	4.2
Pregnancies per initiated cycle (%)	47.4	38.7	30.1	20.3	10.7
Livebirths per initiated cycle (%)	41.2	31.6	22.3	12.4	4.9
Livebirths per retrieval (%)	44.3	35.3	25.8	14.9	6.2
Livebirths per ET (%)	47.2	38.1	28.2	16.7	7.2
Singleton livebirths per ET (%)	30.9	27.0	21.8	14.0	6.6
Cancelled IVF cycles (%)	7.0	10.5	13.7	17.0	20.3
Average ET (*n*) per patient	2.1	2.3	2.7	3.1	3.2

Notes: IVF = *in vitro* fertilisation, ET = embryo transfer. All data derived from U.S. CDC 2009 Assisted Reproductive Technology Report for non-frozen (fresh) transfers involving non-donor gametes. No data were tabulated for patients age >44 years in this report.

If aCGH had been incorporated with IVF in 2009 to facilitate SET (rather than number of transferred embryos being $\geq$ 2), then some of California's 4,810 preterm birth outcomes resulting from IVF would have been replaced by less expensive term singleton deliveries. These adverse preterm outcomes may be avoided, but not eliminated entirely. This is because the background rate of preterm birth in California without IVF is not zero. As Chang and colleagues (2012) have reported, approximately half of all preterm births occur because of unknown factors independent of IVF. Analysis of 2009 California birth data shows a background rate of approximately 20.5% of deliveries being preterm, in contrast to California's preterm birth rate following standard IVF

which is ~63%. While it is not surprising that the aggregate health spend on IVF infants is quite small compared to the majority (non-IVF) infant population, the difference in proportional resource allocation between term and preterm babies is conspicuous (see Figures 3a and 3b). Accordingly, if 7,546 deliveries were attributed to IVF in 2009 (from (c), above) and all of these births resulted from single embryo transfer, then 20.5% of 7,546 would still be expected to be preterm deliveries (Chang *et al.*, 2012). This means that only about 1,547 preterm babies would have been delivered in 2009, instead of 4,810. Avoiding 3,263 preterm births in 2009 would have saved California about $168M in NICU spending.

Assuming the mean delivery cost per preterm infant is $51,600 (from (i), above), then the aggregate delivery costs for 1,547 preterm infants should total about $79.8M. The remaining babies "rescued" as term singleton deliveries from IVF (*n*=5,999) will require about $56M in care costs, for a total of $135.8M in overall delivery costs for all California IVF babies in 2009.

Considering California's actual health spend on the 4,810 actual preterm births from IVF in 2009 was at least $248M, and that the state spent about $25.5M for singleton term delivery, the intervention of single embryo transfer with IVF should recover about $137.7M in NICU overspend for 2009 (see Figures 4a and 4b).

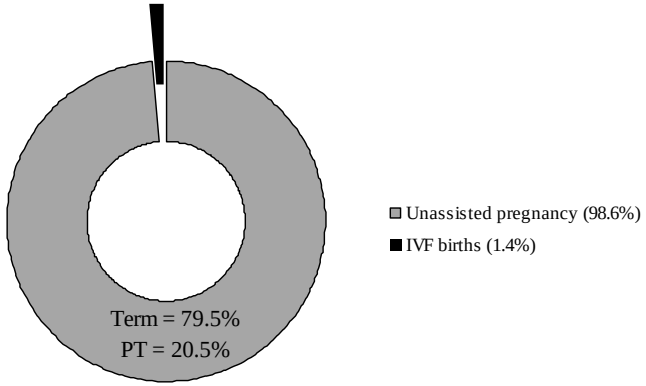

Figure 3a. Total 2009 births in California (*n* =526,774), IVF vs. Unassisted pregnancy (non-IVF).

Source: State of California, Department of Finance (2012). PT = preterm (<37wks at delivery).

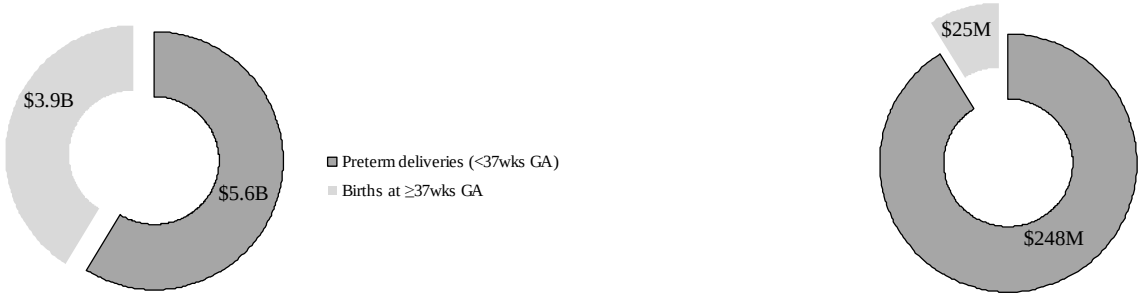

Figure 3b. Distribution of delivery costs in California by gestational age at birth 2009 (calculated).

Background California population/unassisted pregnancy births (left) vs. California IVF births (right)
Source: State of California, Department of Finance (2012) and Sunderam *et al*, (2012).

However, before realising $137.7M in savings, California must first offset the *de novo* costs of IVF with aCGH and single embryo transfer needed to reach this lower preterm delivery target. This means the $137.7M must be reduced by the total amount of state subsidy provided for IVF patients in California. From (j) above, this is $13,000 per treatment assuming no funding match by the IVF patient (because this projection considers only fresh transfers, costs associated with medications, embryo cryopreservation, and subsequent frozen/thaw embryo transfer are not included). Even if every IVF cycle initiated in California during 2009 (*n*=18,405) were matched with state monies amounting to 50% of total treatment cost (*i.e.*, reducing IVF patient out-of-pocket cost by half), the requisite initial investment from California ($119.6M) would be fully recovered and net an annual state revenue surplus of approximately $18.2M.

Likewise, if aCGH had been available and incorporated with IVF to facilitate SET in 2009 (rather than multiple embryo transfer), then some of California's 3,566 multiple gestation births resulting from IVF would have been averted. Among California IVF patients, the observed multiple gestation rate was 47.3% in 2009, which is significantly higher than the 3.2% multiple gestation rate in the general California population.

Thus, if IVF with aCGH and single embryo transfer had been available for all 7,546 IVF cases, then this treatment would not have inflated the multiple gestation rate and instead would have contributed only ~242 IVF births as twins, triplets or higher-order multiple gestation. The avoidance of 3,324 excess (iatrogenic) multiple gestation births (if these

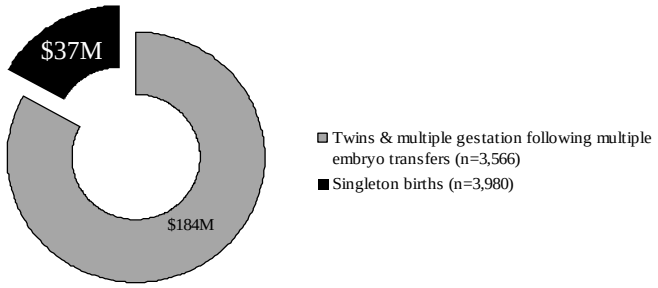

Figure 4a. Distribution of delivery costs associated with 7,546 IVF births in California (2009, calculated).

Total delivery & infant care budget for IVF births = $221M. *Source*: State of California, Department of Finance (2012).

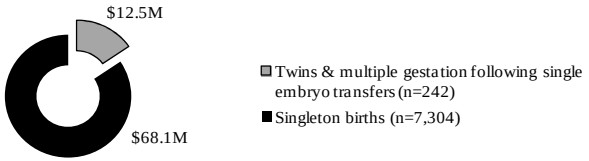

Figure 4b. Distribution of delivery costs associated with 7,546 IVF births in California (2009, calculated). Anticipated total delivery & infant care budget assuming IVF with single embryo transfer = $80.6M.

Source: State of California, Department of Finance (2012) and Sunderam *et al*, (2012).

delivered before 37 weeks gestation and therefore properly classified as preterm deliveries), would yield an even more dramatic realignment of NICU resources. Modifying the previous formula, this may be estimated as follows:

$$H = G(b) \times G(c) \left\{ \begin{matrix} G(tm) \\ + \\ G(<37) \end{matrix} \right\}_{\text{MET}} - G(b) \times G(c) \left\{ \begin{matrix} G(tm) \\ + \\ G(<37) \end{matrix} \right\}_{\text{SET}} - F(c)/2$$

Where *H* is the projected savings recovered from all IVF births under SET conditions subtracted from current IVF deliveries and multiple embryo transfers (MET), factoring the programme cost of IVF. Specifically, delivery care costs in California when IVF is offered with multiple embryo transfers is about $221M (due to the significantly higher multiple gestation/preterm birth rate), compared to only $80.6M if IVF were exclusively performed with SET resulting in no disturbance in the expected 3.2% multiple gestation rate. Again, assuming California's benchmark benefit plan includes a 50% matching formula to discount the patient's out-of-pocket cost for IVF with aCGH by half, (*F(c)*/2, above) all costs to the state would be fully recovered—plus an annual net surplus of $20.9M (see Figure 5).

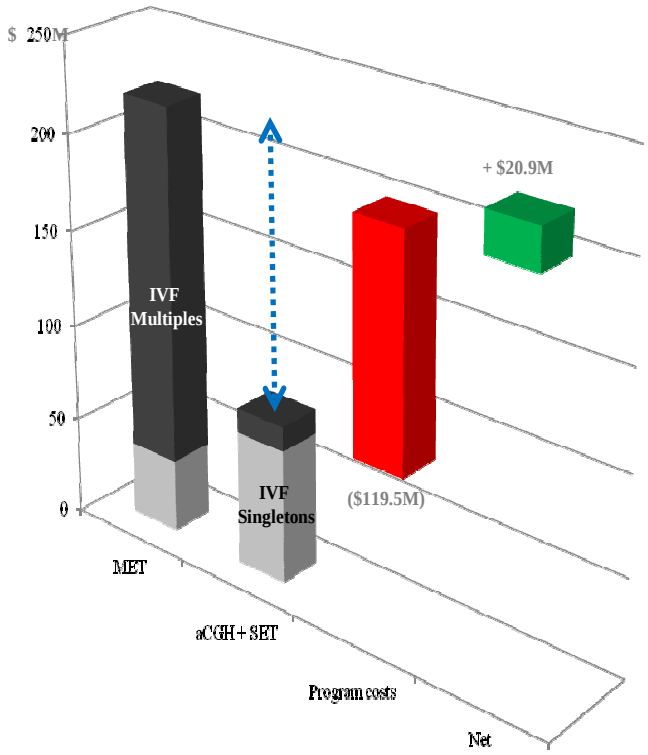

Figure 5. Summary of IVF delivery costs in California (*n* = 7,546) stratified by gestational type, after multiple embryo transfer (MET) or array comparative genomic hybridisation with single embryo transfer (aCGH+SET). The distribution of multiple gestation (dark grey, above) vs. singleton births (light grey, below) after IVF is compared for each embryo transfer approach. Delivery costs are presented in 2009 U.S. dollars (millions).

Since delivery expenditures for singleton births average about 20% of multiple gestation delivery, and because the multiple gestation rate with SET is significantly lower compared to MET, delivery costs following aCGH+SET would be expected to be approximately $140.4M lower using this embryo transfer strategy (dashed line, blue). However, this recovery must be offset by IVF+aCGH expense ($119.5M), before net savings may be estimated.

Assuming treatment fees for all IVF cycles initiated in California during 2009 (*n*=18,405) were supplemented by a negotiated 50% state matching grant (red bar), savings from averted multiple gestation/preterm births after aCGH+SET would be sufficient to defray treatment cost plus provide >$20M in net revenue to California (green bar).

Note that preterm birth and multiple gestation outcomes are not independent events, so the budget recoveries forecast from the two sample calculations above are not additive. Neither state nor federal data presently allow for a regression analysis to show how fresh SET after IVF with aCGH might affect multiple gestation and preterm birth. In other words, some singleton deliveries will still be preterm, and some twin pregnancies may deliver after 37 weeks gestation, but calculating frequencies of these special outcomes is not possible from existing data.

Another matter to consider as embryo testing becomes routinely integrated with assisted fertility treatment is that the clinical effectiveness of IVF changes when comprehensive chromosomal screening of embryos is included. For example, significantly higher implantation rates following transfer of an embryo after genetic testing have been reported by multiple investigators (Schoolcraft *et al.,* 2012; Sills *et al.,* 2012b; Yang *et al.*, 2012) and the effect appears consistent for IVF patients of various ages. This modification means that consumption of IVF cycles could be reduced because successful pregnancy can be reached earlier and with fewer attempts, even in the setting of mandatory SET policy. Using 2009 California data, this effect can be measured by calculating actual IVF treatment yield where 18,405 standard IVF cycles were initiated to give 7,546 deliveries (approximately 41%). In contrast, the pregnancy rate reported with IVF, aCGH and SET is increased to ~70% (Yang *et al.,* 2012). Thus, the initiative described here could have provided California IVF patients all their births in 2009, but with 7,625 fewer cycles initiated—thus redirecting $99.1M of discretionary spending away from excess IVF consumption and back into California's general economy.

Any curtailment in treatment uptake projected from the significantly improved pregnancy rate using IVF with aCGH and SET must be balanced by the potential for heightened demand in California, a reasonable expectation if patient cost for this service is suddenly reduced by half. Even as total costs for IVF have increased over time, the number of patients seeking this treatment has continued to grow (Talaulikar & Arulkumaran, 2012). It is plausible that a sizable, latent population considering IVF which had previously deferred this treatment due to its excessive cost would now find it

more affordable, thus swelling demand substantially. Administrative intake procedures including defined medical eligibility requirements, proof of California residency, or mandatory waiting periods should be developed to maximise treatment benefit.

Importantly, this proposal would not preclude or proscribe continued privately-funded IVF for patients who wish to maintain the status quo and pay for fertility treatment themselves. Conserving an open-market option for California's private-pay IVF patients should not significantly attenuate the savings projected here. This is because when given the choice of a high pregnancy rate (~70%) from IVF with screened single embryo transfer as provided under the state IVF programme, some affluent California patients may regard this incentive as sufficiently strong to leave the private market. In the private-pay setting, aCGH with single embryo transfer has recently become an option, albeit underutilised. It may be that private insurance contracts eventually move to this model as a condition of assisted fertility treatment coverage, if these policy holders remain as the only residual sub-group of IVF transfers which continue to result in higher-order multiple gestation outcomes.

The estimates discussed here are not without limitations. For example, the reports from which they are derived used surveillance data reported for each IVF procedure performed (not for individual IVF patients), so this analysis could not link procedures for patients who initiated multiple IVF cycles. Also, the contribution of IVF to multiple gestation may be overestimated because stillborn infants were included in the tabulation of multiple births. Perhaps most importantly, data are available only for individuals

seeking IVF during the study period, and cannot ascertain individuals or couples with infertility who did not avail of IVF for personal, financial, or other reasons. Note that these calculations are based on a hypothetical 50% state subsidy to enable IVF treatment for California patients at a level where out-of-pocket costs would be cut by half. Other funding formulas are conceivable. While some patients may still not be able to afford IVF even at the discounted rate with government assistance from California, the impact of demand elasticity and price-for-service was outside the scope of this analysis. Except for industry reports that are not publicly available, very little data exists on individual consumer demand and personal income as reported by IVF patients. Notwithstanding these limitations, the projections here can provide an essential starting point for policy debate.

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5. Bioethical Considerations & Reproductive Policy Concerns

Studies of public opinion and social response concerning offering access to a state subsidised IVF program where "terms and conditions" apply are underway, but the proposal's public reception in California is likely to be favourable and similar to that presently voiced in support of conventional IVF. To be sure, even established health policies regarding reproductive issues rarely meet with universal acclaim (Dickens, 2005) and some criticism from religious, feminist, or disability-rights advocates could follow this initiative. Perhaps the most controversial aspect of the current proposal entails setting boundaries on how information obtained from comprehensive chromosomal screening of embryos may be used.

For example, recognising that IVF patients desire a healthy child from their pregnancy, what will be the disposition procedure for any abnormal or diseased embryos which the state has helped identify by aCGH (Piyamongkol *et al.*, 2006; Altarescu *et al.*, 2011)? Should state resources be part of a treatment which allows IVF patients to select the sex of their offspring (Sills & Palermo, 2002b)? Could IVF patients use this programme to begin a pregnancy expressly to have a "tissue matched" baby, so that a suffering, older sibling requiring a transplant might have a donor and survive (Samuel *et al.*, 2009; Lai, 2011)? Can the programme be expanded to include IVF with donor gametes, and, if yes, how will the matter of donor compensation (if any) be resolved? Such concerns raise sensitive and complex questions when basic IVF is funded entirely at patient expense; involving public money will no doubt focus increased attention on these bioethical

issues and will require considerable multidisciplinary input to settle (Farsides & Scott, 2012).

Yet in 2004, the California public encountered a question of related complexity. Voters were asked if public funds should be used to support controversial, high-technology biomedical research. “Proposition 71” established the California Institute for Regenerative Medicine to award $3 billion in competitive, peer-reviewed grants to advance stem cell research (including human embryonic stem cell work). Authorising the most expansive state-funded medical research initiative in U.S. history, this ballot initiative passed with nearly 60% support (Burgin, 2010). Although implementing partial state subsidies to enable IVF treatment in California with aCGH and SET as proposed here would require a far smaller budget (and would provide clinical results much sooner), it would not be free from its own administrative challenges.

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6. The Economics of IVF & Insurance Under 'Obamacare'

The financial stress associated with IVF is difficult to overstate. Prohibitive out-of-pocket costs make many who need IVF unable to initiate or complete this therapy. The clinical or institutional expense is, unfortunately, just one aspect of treatment since pharmacy costs associated with IVF often increase substantially the overall expense to patients. Research suggests that fertility patients will sometimes choose to self-administer more of the prescribed injections, if it might mean saving enough money to make IVF more affordable (Sills *et al.*, 2012a). Although previous research has shown that gonadotropin use during IVF may be lower where SET is mandated (Salame *et al.*, 2011), this cost element was not included for coverage in the proposed initiative for California. Previous research has recognised the challenge of gonadotropin cost and others have outlined workable strategies to include this expense in an overall IVF budget (Hildebaugh *et al.*, 1997; Stassart *et al.*, 2011). Should actual health savings for California exceed projected levels, then a pharmacy benefit could be added in a subsequent revision.

In the fortunate circumstance where individuals do have access to IVF either by a mandatory state requirement or a defined employee health benefit to offset these treatment costs, patients are acutely aware of the vulnerable nature of such coverage. Access to IVF, and therefore the ability to begin or grow a family, will be disrupted if patients move to another state or if they lose their job. This pressurised situation helps explain why some patients are not dissuaded from IVF merely because a twin pregnancy could result. Multiple studies have demonstrated that a twin outcome from IVF is not

only acceptable, but desirable (Gleicher & Barad, 2009; Walsh *et al.*, 2009a; Fiddelers *et al.*, 2011).

Even when the number of transferred embryos is limited to two (a policy generally regarded as conservative clinical practice in USA), the risk for dizygotic twinning after IVF must be acknowledged as significantly higher than the twinning risk observed in a background population of unassisted conception (Sills *et al.*, 2000 & 2010d). IVF patients are informed that health costs for twins and triplets may be 3- and 10-fold higher, respectively, compared to singleton deliveries (Ledger *et al.*, 2006), but in clinical practice this rarely dampens the enthusiasm for twins (Gleicher & Barad, 2009). One reason consumers may be focused more on attaining "pregnancy at any cost" is that after delivery, the reimbursement system changes so that supportive care, infant surgery, and other neonatal health resources become covered expenses, eligible for state support or insurance coverage. In other words, while treatment expense for IVF in California is almost always funded privately, the substantial downstream costs deriving from any multiple gestation or preterm births are shared by society.

Linking insurance coverage or state subsidy with the objective of improving access to IVF is not an entirely new concept. In the United States, however, a SET stipulation as a condition of assistance with IVF treatment does not currently exist, most likely due to inadequate technology to identify reproductively competent embryos with precision. Even in states where insurance coverage for IVF is mandated for certain groups (*e.g.*, Illinois, Maryland, Massachusetts and Rhode Island), SET is not compulsory. Elsewhere,

the provision of IVF is on the basis of the patient's own ability to pay (Neumann, 1997). It was against this backdrop that "Obamacare" entered the national vocabulary to describe a method to provide substantial and serious reforms for the American healthcare system.

On June 28, 2012, the Supreme Court of the United States issued a landmark ruling in the matter of *National Federation of Independent Businesses v. Sebelius* (2012), which challenged the constitutionality of the Patient Protection & Affordable Care Act, 2010 (PPACA). This 5-to-4 decision affirmed the constitutionality of key elements of "Obamacare" and returned the national discourse on universal healthcare back to the political arena (Friedman, 2012). While the Court cleared a significant obstacle for providing universal healthcare in USA, it was not designed to consider specific types of treatment which should be provided. In fact, neither "Obamacare" itself nor the ruling from the nation's highest Court provided any guidance to American fertility patients. For patients seeking elective fertility treatment, the most important changes brought by PPACA are that lifetime limits ("benefit caps") for covered services were eliminated, and that pre-existing conditions cannot be used as a basis to deny health insurance coverage (Bazer, 2012). Coverage areas under "Obamacare" were reserved for the U.S. Secretary of Health and Human Services (HHS) to define, and this federal department established the essential health benefits (EHB) across ten categories as shown in Table 5.

In compliance with the PPACA, each state has nominated its own insurance model in accord with this ten-part framework, to define the minimum coverage offered by all

insurers operating in that particular state. As expected, the role of the EHB was immediately recognised as central to the practical deployment of "Obamacare" since the EHB is the local mechanism by which each state defines patient benefits. With many vested interests in play (and frequently in open competition with each other), negotiating the EHB became a politically and socially charged endeavour (Iglehart, 2011).

Table 5. Health insurance coverage areas required by the U.S. Patient Protection & Affordable Care Act, 2010

(1) Ambulatory patient services
(2) Emergency services
(3) Hospitalization
(4) Maternity & newborn care
(5) Mental health & substance use disorder services (behavioural health treatment)
(6) Prescription drugs
(7) Rehabilitative and habilitative services/devices
(8) Laboratory services
(9) Preventive/wellness services and chronic disease management
(10) Paediatric services, including oral and vision care

An expert panel recommended that a "structured interactive process" be developed at the federal level to advise HHS on balancing the "tensions between comprehensiveness and affordability." This committee consistently recognised that if the chronic problem of

rising health care costs were not adequately addressed, the most laudable goal of PPACA—to help the uninsured American population—is likely to be undermined.

California's essential health benefit was codified in Senate Bill (SB) 951, signed by Governor Edmund G. Brown Jnr. on September 30, 2012. This mandated that all small group and individual health insurance policies issued, amended, or renewed in the State of California must be identical to the health benefits covered by the "Kaiser HMO 30" plan (see Table 6), effective January 1, 2014 (State of California, 2012a). The legislation also prohibits any California insurer from modifying the list of mandatory benefits, even if such substitutions are budget neutral (State of California, 2012b).

Because the benchmark plan selected by California specifically excludes the advanced reproductive technologies, fertility patients in California cannot look to "Obamacare" to improve access to IVF treatment at this time. The enactment of SB 951 does not mean that California is prohibited from including IVF in its "Benchmark Plan" in the future, only that there is no mandate for California to do so now. Benefits and services can be modified by the California General Assembly in 2015. As data from new technologies become available, each state's benchmark plan is encouraged to be "more fully evidence-based, specific, and value-promoting over time" (Institute of Medicine, 2011). In California, this directive could be influenced by one recent study of more than 90,000 fresh, non-donor IVF cycles comparing outcomes between states that mandated IVF coverage with those that did not (Martin JR *et al.*, 2011). Interestingly, "free-market" states (no mandate) achieved a higher pregnancy rate (38.8% vs. 35%) and live-birth rate

Table 6. California's State EHB 'Benchmark Plan' (SB 951), 2012 Coverage detail.

Component	*Cost to Patient*
Annual deductible	0
Pharmacy deductible	250 for non-generic (brand) prescriptions
Annual out-of-pocket maximum (individual/family)	3,000/6,000
Clinic visits (unless only for preventive & maternity)	30 co-payment
Preventive care & PNC	0
Infertility treatment (IVF, ICSI, TESE)	[*Excluded*]
OT/PT & speech therapy	30
Most laboratory tests & basic radiology	10
MRI/CT/PET (complex radiology)	50
Outpatient surgery	200/procedure
A&E visits (waived if direct hospital admission)	100
Ambulance	75
Prescriptions – generic equivalent	10 (up to 100-day supply)
Prescriptions – brand specific	35 (after pharmacy deductible)
Hospital care – accommodation, tests, supplies, therapies	400/day
Hospital care (up to 100 SNF care days)	0
Mental health services – outpatient	30 individual/15 group
Mental health services – inpatient	400/day
Chemical dependency services – outpatient	30
Chemical dependency services – inpatient (detox only)	400/day
Select DME, prosthetics, orthotics, optical	Not covered, but 20% off on glasses & contacts purchased from Kaiser
Vision exam	0
Home health care (up to 100 2hr visits)	0
Hospice care	0

All costs reported in US$ (2012).
Notes: EHB – essential health benefit, SB – Senate Bill (California General Assembly), PNC – prenatal care, IVF – *in vitro* fertilisation, ICSI – intracytoplasmic sperm injection, TESE – testicular sperm extraction, OT/PT – occupational therapy/physical therapy, SNF – skilled nursing facility, DME – durable medical equipment.

(32.2% vs. 29.1%) than states with an IVF mandate, but these results came at the expense of a significantly higher twin (28.1% vs. 26%) and triplet rate (3.9% vs. 3.4%) in the nonmandated states. Not surprisingly, the mean number of embryos transferred was significantly higher among nonmandated states (2.6 vs. 2.2).

California leadership could find guidance from prior research on mandated IVF coverage, the transfer of fewer embryos, and lower rates of multiple pregnancies and births, particularly in the younger age groups (Martin JR *et al.,* 2011). It should be emphasised that such results from IVF were attained in the absence of any routine comprehensive chromosomal screening of embryos. Outcomes with standard elective SET (without any genetic assessment to guide which embryo is selected for transfer) can permit subsequent FET cycles, where a single thawed embryo is transferred on each occasion. Although this approach can work for some patients (Milne *et al.*, 2010), for any one transfer SET has been found to yield about a one-third loss of success rate relative to dual embryo transfer (Roberts *et al.,* 2010), and necessarily increases the "time to pregnancy" and overall treatment interval for IVF patients.

A key recomm1endation of the IOM Committee on Defining and Revising an Essential Health Benefits Package for Qualified Health Plans (Institute of Medicine, 2011) specifically states that, beginning in 2015, the HHS Secretary should update the EHB package to make it more fully evidence-based, specific, and value-promoting, with an emphasis on cost analysis. For California, "Obamacare" will almost certainly result in significant additional demand for healthcare as more women gain insurance coverage

(Gee & Rosenbaum, 2012), and the funding for these extra services will need to come from somewhere. Regarding first-year-of-life care for multiple gestation and preterm birth, California already allocates considerable resources to provide these services. The data presented here show that aCGH with IVF and SET is one way to lower the healthcare burden associated with some of these “super-utilisers”, so that the millions of dollars saved could be used to offset partially the costs of other State of California care obligations enumerated by “Obamacare”. Just as with empirical research in other disciplines, it will be impossible to audit uptake of any social service until it has been identified, measured, and defined (Webley, 2010); a public deliberative process should inform choices about how to configure the updated package (Igelhart, 2011). It seems unlikely that the U.S. Health Secretary will modify the EHB to include fertility services at the federal level, but the State of California will have more flexibility.

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7. IVF and Population Growth

What is the source of American population growth? Only about 1 in 75 new births in the United States is from IVF (Fuller, 2012). In contrast, the foreign-born population in the United States has tripled since 1970 (Capps *et al.*, 2005). Even though a tiny minority of Americans avail of IVF and its traditional multiple embryo transfers, the number of IVF cycles initiated has increased every year since the treatment became available. In the meantime, the frequency and pattern of multiple births has changed dramatically, with the twinning rate rising 70 percent between 1980 and 2004 (Martin JA *et al.*, 2011). Perhaps paradoxically, this upward trend in multiple gestation has occurred against a background of gradually falling national fertility rates. For example, the total U.S. fertility rate was 2.0 births per woman in 2009, but this dropped to 1.9 the next year and is now well below the replacement fertility level of 2.1. Similar changes (declines or plateaus) of fertility rates have been reported in Ireland, Italy, Spain, Sweden, and other European countries (Mather, 2012).

Declining fertility in the U.S. is primarily being driven by a trend among young adults to postpone childbirth (Mills *et al.*, 2011). That so many of these individuals become IVF patients, and eventually mothers to twins, triplets, and higher-order multiple preterm births, is reflected in the delivery statistics discussed previously (Talaulikar & Arulkumaran, 2012). In 1970, births among women in their 20s were significantly more numerous than those from women in their 30s. But, by 2009 the birth rate among U.S. women ages 30 to 34 (97.5 births per 1,000 women) exceeded that for women ages 20 to 24 (96 births per 1,000 women)—a major demographic shift for the United States.

Among very young mothers in the U.S., the same pattern is evident: the (2010) birth rate among teens dropped to 34 births per 1,000 females ages 15 to 19—the lowest level ever recorded for this group in the United States (Mather, 2012).

As impressive as IVF technology may be, attention to the opposite end of the life spectrum finds changes even more consequential for population growth. Quite independent of IVF utilisation (but not entirely unrelated), human mortality has decreased so substantially that the difference between hunter-gatherers and our lowest mortality populations is now greater than the difference between hunter-gatherers and our closest evolutionary ancestors in the animal kingdom, the wild chimpanzee. Most of this reduction in human mortality has occurred since 1900, experienced by only about four of the approximately 8,000 human generations that have ever lived (Burger *et al.*, 2012). As infertility was once though intractable, the concept of old-age mortality also has been significantly re-focused (Sills *et al.*, 2001), such that life expectancy is no longer approaching a limit. Indeed, current evidence suggests that human ageing is plastic (Vaupel & Kistowski, 2005) and that survival may be extended by various genetic changes and non-genetic interactions.

These demographic observations still must consider pro-natal technologies such as IVF carefully, because fertility and mortality are the two critical factors determining population size and age structure, and these usually do not change abruptly without famine, pandemic, or war (Feng, 2012). One exceptional case is China, where 30 years of severe policies limiting births (Sills *et al.*, 1998) have had the dramatic effect of

curtailing population growth to among the lowest in the world (Feng, 2012). But in any country, reduced fertility coupled with rising longevity will cause the proportions of elderly to increase sharply and limit the supply of youthful labour to some extent. Even the oldest national populations of today will experience a doubling or more in their old-age dependency ratios in the coming decades (Lee & Mason, 2010) irrespective of IVF utilisation. For populations with low or negative growth, policies to address ageing and very low fertility are of central importance. The current proposal addresses the fertility component to harmonise with other calls to improve efficiency of health spending, to strengthen social groups, and to empower individual fertility decisions (Ezeh *et al.*, 2012).

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8. Conclusion

The U.S. population is now characterised as decreasingly fertile, but with more multiple gestation births and significantly longer lifespans compared to prior generations. Acting with other socioeconomic factors, these characteristics exacerbate an unprecedented crisis in the American healthcare system. No single proposal can expect to address all facets of America's healthcare budget crisis. Yet, key sectors must be encouraged to implement creative solutions in their domain with a view to manage costs more effectively. Here, comprehensive chromosomal screening of embryos on day five, integrated with IVF and single fresh embryo transfer is proposed for California to resolve two distinct but interrelated health system objectives: Reduction of "first year of life" health spending associated with multiple gestation and preterm births from IVF, and, equalisation of access to IVF without regard to ability to pay by means of a qualified state subsidy. It is unusual when two healthcare problems are fixable with a single policy initiative; it is exceptional when that policy conserves resources which are already limited.

Reducing public health spending remains the focus of some budget strategies, and application of an integrated aCGH protocol with IVF and fresh SET should warrant consideration. Although extended embryo culture and blastocyst transfer are often considered as a way to "naturally select" embryos (Sepúlveda *et al.,* 2011), this strategy has a low efficiency in identifying euploid embryos for transfer. In America, individual states can develop unique public health insurance programmes which may be used as experimental models influencing the entire nation (Larson & Williams, 2003; Romney,

2007). The present analysis is the first to demonstrate how a social health investment by California in IVF, aCGH from embryos biopsied on day five, and fresh SET being can be more than recovered by downstream savings, because health spend is conserved when costs of higher-order multiple gestation deliveries are avoided in favour of singleton births from IVF. This approach will not be considered in a policy vacuum, and other initiatives can also help by working in a complementary manner. For example, S965 in the U.S. Senate/HR 3522 in the U.S. House of Representatives (the "Family Act") is one legislative effort which creates a new federal tax credit for infertility patients. The proposed credit would be based on 50% of IVF out of pocket costs, up to a lifetime maximum benefit of $13,360 (U.S. Library of Congress, 2012). A federal tax credit as proposed by the "Family Act" could be coordinated with a related state initiative in California to emphasise the role of aCGH and SET with IVF.

Until aCGH emerged as a reliable and precise procedure to identify reproductively competent embryos in IVF, any reproductive health policy mandating SET would be impractical and poorly accepted by consumers. This proposal shows how rapid, on-site aCGH can bring single embryo transfer IVF pregnancy success rates approaching 70% within reach (Sills *et al.*, 2012b; Yang *et al.*, 2012) even for poor prognosis IVF patients (Liu *et al.,* 2012b). Now that such data are available, it is essential that patients, providers, and policymakers understand the hazards (medical and economic) of continued multiple embryo transfer with IVF (Sills & Collins, 2013). California's EHB schedule, set for revision in 2015, should include an economic analysis of statewide hospital encumbrances associated with neonatal "super utiliser" births after IVF

treatment. Specifically, for every preterm birth averted when SET is performed, California's downstream health spend per infant could be reduced by about one-fifth ($51,600 vs. $9,329). While other states already require insurance coverage for IVF, none address the multiple gestation or preterm birth problem by restricting the number of fresh embryos transferred after comprehensive chromosomal embryo screening. California can do better. Cost recovery in California's health spending can be achieved with a pilot programme providing this service for qualified residents.

California's investment in aCGH with IVF and SET makes economic sense because the initial fertility treatment cost is always dwarfed by the subsequent healthcare burdens associated with preterm birth and multiple gestation. If a 50% matching program for IVF with aCGH and SET were available in California as proposed here, the grant amount per patient ($6,500) would be an effective way to reduce the state's rate of preterm and multiple gestation births in this population—thus reducing the frequency of (and possibly mitigating maternal requests for) cesarean delivery (D'Souza & Arulkumaran, 2013). The approaching 2015 target to modify the California Insurance Code (benchmark health plan) presents an opportunity to recast the regulatory framework to enable this approach. Additional impact studies are anticipated to validate policy goals and to determine administrative procedures to facilitate implementation as the EHB revision date nears.

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10. Appendix – Author's 2003-2013 publications cited in this thesis

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