I’m giving you draft pieces from a book manuscript. The book, under contract to the Harvard University Press, is tentatively entitled THE END OF SEX: THE FUTURE OF HUMAN REPRODUCTION. It is also about 18 months late to my long-suffering editor. As I write this I am halfway through chapter 16 of 18; the whole draft should be done by the time I present this as a talk to you, though the hard work of rewriting (mainly pruning) will remain.

I’m sending you the table of contents, the overall introduction, two "interludes" (small transitional chapters between Sections I and II and Sections II and III), and the introduction to Section III. They add up to about 37 double spaced pages and I hope they are easy to read. The table of contents and introduction should be enough to give people some idea of what I’m doing; the second interlude (EoS11xInt2) is the longest piece I’m sending, the most substantive, and the one I must urge you to read.

This is still a draft – please do not cite or quote it without permission (which I hereby give for any class assignments for which it is relevant). I look forward to discussing it with you on March 24.

Hank Greely
The End of Sex: The Future of Human Reproduction

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Introduction

This is a book about the future of our species, about deep ethical and legal challenges our societies will face, and about the likely development of revolutionary biological technologies. But the best way to sum it up, I think, is to say that it is about the coming obsolescence of sex.

It is not about the disappearance of *all* the things we mean by the word “sex.” Humans will still generally appear at birth having physical attributes of one sex or the other and will be loudly pronounced as either baby girls or baby boys, with the appropriately colored accompaniments. Our descendants will still (usually) have genetic contributions from both an egg and a sperm, thereby achieving the mixing of parental genes that is also sex, or, at least, sexual reproduction. And, I predict, people will continue to practice sexual intercourse in a myriad of different ways and for almost all of the current different, complicated (and uncomplicated) reasons.

But I believe that, sometime in the next 20 to 40 years, sex in one sense will largely disappear, at least among the majority of humans with good health coverage. People will no longer use sexual intercourse to conceive their children. Instead of being conceived in a bed, in the backseat of a car, or under a “keep off the grass” sign, children will be conceived in laboratories. Eggs and sperm will be united through *in vitro* fertilization (IVF). The DNA of the resulting embryos will then be sequenced and
carefully analyzed before decisions are made (passive voice intentional) about which embryos to transfer to a uterus for possible development to a living, breathing baby.

In short, we humans will begin, very broadly, to select consciously and knowingly the genetic variations, and thus at least some of the traits and characteristics, of our children. This idea is not new. It has been a subject of hundreds, probably thousands, of stories and novels – BRAVE NEW WORLD by Aldous Huxley was not the first, but it was certainly the first truly memorable one. It has been the subject of other forms of fiction, notably the 1997 movie GATTACA. And it has been the subject of tens of thousands of books, articles, sermons, and other non-fiction analyses – usually viewing with alarm, but occasionally pointing to with (prospective) pride.

This book is different. It is not, primarily, a discussion of the consequences of such a world (although it does try to analyze them to some extent). It is a description of precisely how and why that world is going to arrive. Two insights drive this book. The first is the way new techniques, drawn from several different areas of modern bioscience research, will combine to make this future not just possible but cheap and easy. The second is the way economic, social, legal, and political forces will combine to make this future not just possible, but, as I believe, inevitable. Those insights turn these questions from interesting, and somewhat goosebump-inducing, speculations to real problems that will confront real people – us and our children – in the next few decades.
The technical innovations will come from two worlds: genetics and stem cell research. We can already do preimplantation genetic diagnosis (PGD) on embryos. We can take away one cell of an early embryo, test it for a genetic trait or two, and use that information to decide whether to give it a chance to become a baby. That technique, preimplantation genetic diagnosis, has been used for two decades – the first child born after PGD is now over 22 years old. And every year now, around the world, thousands of new children are born following PGD.

But today PGD is weakly informative, expensive, unpleasant, and even dangerous, thanks both to the limitations of genetic testing and to the necessity of using IVF as part of PGD. These constraints will change. Genetics will allow us to do cheap, accurate, and fast sequencing of the entire 6.4 billion base pair genome of an embryo and will give us an increasingly deep understanding of what that sequence means for disease risks, physical characteristics, and other traits of any child that embryo becomes. And stem cell research will allow couples to avoid the expensive and (for the women involved) unpleasant and physically risky process of maturing and retrieving human eggs by allowing us to make eggs (and sperm) from stem cells. The result will be a cheap, effective, and painless process I call “Easy PGD.”

Of course, just because technological innovations are possible does not mean they will be adopted. The supersonic commercial jetliner came and went; the flying car and the rocket backpack were never really launched, though both are technically feasible. I argue that, unlike those technologies, Easy PGD has a clear path to acceptance in the
United States and likely paths to adoption in some other countries. It may not be approved everywhere, but in an increasingly global world, that could well be irrelevant.

The ideas in the last few paragraphs are the core of this book. I will also discuss some of the potential consequences that widespread adoption of Easy PGD has for individuals, for families, for societies, and for humanity. Those fields have been frequently plowed before; I hope the specificity of my method of parental trait selection, as well as the near immediacy of the questions it raises, may add some value to my analysis over those that have come before me.

Concretely, the book is divided into three parts. Part I provides background information on the science and technology involved in Easy PGD. It provides a nonscientist’s guide to the varied ways living things reproduce; to the specifics of how humans reproduce, naturally and by IVF; to DNA, genes, chromosomes, and genetic testing; and to stem cell research. Part II explains how and why Easy PGD will happen, looking first at the technical developments in genetics (or genomics) and in stem cell science and then at the medical, economic, legal, and political factors that will make it not just acceptable, but widely adopted. Part III examines the broader implications of Easy PGD. It looks at issues of safety, coercion, equality, family, and nature, along with some other, more varied consequences of the technology.

My editor and I have had some disagreements about this book. She wants me to make an argument – to take a position and fight it out, guns blazing. But I’m a law
professor, trained as a lawyer. Lawyers do many things. Sometimes they argue zealously in court for their clients’ positions, whether they believe them or not. But sometimes they lay out all the facts and implications, as they see them, for the clients to make their own decisions. I have some views about ways we might regulate Easy PGD, but they are tentative, based on glimpses and guesses of the future and on my own preferences and principles. I will not insist on them. But I will ask that you develop opinions. Easy PGD will give prospective parents – including perhaps some of you – more choices but will set some hard questions for all of us. My goals are first, to get you interested in those questions – as parents, as grandparents, as citizens, as humans – and second, to give you information to help you reach your own conclusions.

Aldous Huxley’s famous novel takes its title from one of Shakespeare’s last plays, *The Tempest*. Years before the play starts, plotters abandon Prospero, who is both Duke of Milan and a magician, at sea with his infant daughter, Miranda. They survive on an island with only inhuman company. The years go by; Miranda grows up, and fate and Shakespeare deliver the plotters to the island and into Prospero’s hands. Miranda sees them, almost the very first humans she has ever seen, and, not knowing that they had long ago plotted her death along with her father’s, she famously exclaims:

O, wonder!

How many goodly creatures are there here!

How beauteous mankind is! O brave new world,

That has such people in't!
That is often remembered. What few recall (though I am sure Huxley did) was Prospero’s immediate reply: “‘Tis new to thee.” My hope is that when Easy PGD opens the prospects of some kind of brave new world, you will be more knowledgeable, and more sophisticated, than Miranda. (Though things do work out well for her, in the end.)
First Interlude

Easy PGD – The Possibilities

The first six chapters of this book have given you some background on some fairly disconnected parts of biology and human medicine – genetics, reproduction, infertility treatments, and stem cell research. I believe those threads will soon develop in new ways that will come together to form a new pattern, one that will change fundamentally how our species reproduces.

I call the process that will emerge from these developments Easy PGD. It is fundamentally just an extension of preimplantation genetic diagnosis, but an extension that will turn PGD from a rare curiosity to the way most babies will be conceived.

PGD is currently used only to look at a few genetic or chromosomal issues. It can tell prospective parents about whether their embryos are aneuploid or euploid, of concern in part for Down syndrome and in part for the likely success from transferring any particular embryo. It can also be used to look at a genetic disease that runs in the family – Huntington disease, sickle cell anemia, Tay-Sachs, or some other dread condition.

But our ability to do genetic analysis – cheaply, accurately, and quickly – is expanding dramatically. Sequencing one whole human genome cost $500 million a decade ago. It cost $50,000 in 2009. It cost under $4,000 in 2012. The cost will soon be in measured in hundreds of dollars, not thousands. And in 20 to 40 years, that cost may
well be expressed in two digits – or fewer. Doing whole genome sequencing from one embryonic cell will not only be feasible, but will be cheap. With sufficient precautions, it should also be accurate. When PGD can look at a whole genome and not just a karyotypes or one particular genetic disease, it will become much more interesting to prospective parents.

At the same time, our knowledge of the connections between genetic variants and traits or diseases is already large. It will become vast. It is unlikely ever to be a perfect predictor for most of the things parents will care about, but it already is perfect, or near perfect, for some things parents prize, like “boy or girl?” Combine whole genome sequencing with a stronger ability to predict phenotypes from genotypes and PGD will only become increasingly attractive. And not just to parents, but also to health insurers or government health programs that can project saving money on the care of sick children by paying for prenatal genetic diagnosis.

But no matter how attractive PGD becomes, its current form has a serious problem. It requires IVF and IVF is not an attractive prospect. IVF is expensive, unpleasant, emotionally trying, and physically risky. People use IVF because it is the only way they can hope to become pregnant, or because they know their children are at high risk for a terrible genetic disease. The problems of IVF, though, are almost all the problems of egg harvest. Getting human sperm is almost always easy; getting human eggs is always hard. Egg retrieval accounts for about 80 percent or more of the cost of IVF, almost all of the discomfort, and all of the health risk.
“Easy” PGD will be easy because it will avoid egg retrieval. Instead, prospective parents will provide some of their cells – probably skin cells – that a clinical laboratory will transform into undifferentiated iPSCs. These iPSCs will in turn to be re-differentiated into gametes: eggs, primarily, but also sperm when necessary. These gametes will be made from the prospective parent’s own cells and own genomes. They will hold out the prospect of have “a child of our own” without the difficulties of egg retrieval – and with the advantages of PGD. Eggs from iPSCs will make PGD easy and easy PGD will transform the world.

With Easy PGD, it will not just be the infertile or those haunted by a family genetic disease who will want PGD. It will be almost anyone. And this will include some possibilities not currently available. Infertile people who do not have their own gametes – whose eggs or sperm never developed or were destroyed or poisoned by accident or disease – will have, for the first time, a chance to have a “child of their own.” And, in the not likely event that iPSCs can make not only eggs from women and sperm from men, but sperm from women and eggs from men, gay and lesbian couples will, for the first time, have a chance to have “a child of their own.”

The science for safe and effective Easy PGD is likely to exist sometime in the next 20 to 40 years. The scientifically possible does not always happen or, if it does happen, persist– consider flying cars or supersonic commercial aircraft. Easy PGD, though, will have favorable medical, economic, social, legal, and political factors, at least
in the United States. Its reception will prove more negative in some other countries, but also more positive in others.

The next five chapters of this book expand on this roughly outline, specifying the scientific progress – and, equally importantly, the social factors – that I believe will transform Easy PGD from science fiction into a large and important reality.
Second Interlude

Easy PGD: The Future

“It is always hard to predict things, especially the future.”

Attributed to Niels Bohr¹

The last five chapters have laid out the pathway to the future. What is at the end of that path? I believe the answer is a world where most pregnancies, among people with decent health coverage, will be started not in bed but in vitro, and where most children have been selected by their parents from several embryonic possibilities based on the genomic variations of those embryos and hence the genetically-influenced traits of the eventually children. This will not happen overnight. Even if all the scientific developments necessary happened tomorrow, the FDA process (or its equivalent in other countries) would likely take a decade or more. And the scientific developments will not happen tomorrow. Even once the technologies are approved, their widespread adoption will take more time. Twenty years is a realistic lower bound for this future; forty years is, I think, a realistic upper bound. This brief section sets out what reproduction is most likely to look like in that future world, as well as the most foreseeable blockages to, and variations in, that future.

The Most Likely Future

¹ This line has been attributed to a wide variety of people, including Yogi Berra, but it is most clearly connected to Danish physicist, Niels Bohr. Unfortunately, no one has located any place where Bohr wrote it. See discussion in Henry T. Greely, Trusted Systems and Medical Records: Lowering Expectations, 52 Stan. L. Rev. 1585, 1591–92 n. 9 (2000). There is also some evidence that this is a Danish proverb, though, if so, it might be a proverb that Bohr started.
Assume Easy PGD, or its constituent parts, are approved by the FDA (or equivalent regulatory authority) and have not, in whole or significant part, been banned on moral grounds by legislation. What happens?

First, IVF clinics will offer Easy PGD. They will form alliances with genetic testing laboratories, just as they have done already for PGD, unless the technologies become easy enough to bring in house. They will either do gamete derivation in house or collaboration with physicians or laboratories that do stem cell derivation. It remains quite unclear who will actually do stem cell derivation when it becomes a clinically useful technology. It seems most likely that laboratories, either distributed locally or large corporate regional facilities, will ultimately do the work of turning stem cells into therapeutically useful derived cells, but whether IVF clinics end up developing that capacity internally depends on its cost and difficulty.

Prospective parents – married or unmarried, gay or straight – will make an appointment with the local clinic to decide whether they want the service. They will have sent ahead copies of (or, more likely, electronic access to) their own entire genomes and their first conversation at the clinic will include some discussion of what diseases or traits their embryos might carry. If the technology has developed sufficiently, this might include discussion of possible gene transfer or synthetic biology to give their children alleles they lack. If the prospective parents decide to proceed, at that meeting or shortly
thereafter, the clinic will take a skin biopsy (or possibly other, even less intrusive cell selection methods) and being the process of deriving the relevant gametes will be started.

Several weeks later, the gametes will be ready and fertilization can proceed. If both eggs and sperm were derived, no further visits will have been necessary for the gametes. (The woman who is to carry the pregnancy may need to be seen in order to synchronize her period with the date when the embryos will be transferred into her uterus.) If only eggs were derived, the male who is providing the sperm will have had to make a visit to the clinic to provide a sperm donation.

At this point, the key question – presumably answered earlier – will be how many eggs to fertilize and, effectively, how many embryos to create. This will not be limited by the supply of eggs, effectively infinite, or of sperm, millions of which can be found in a normal man’s ejaculate. It is more likely to be a decision made based on the costs of analyzing each embryo’s genome, as well as some statistical analysis of the number of embryos necessary in order to have a great likelihood of getting some without serious disease risks. Both of these factors may well vary from couple to couple; some couples may be willing to pay more to check more embryos, some couples at particularly high risk of genetic diseases may need to make more embryos in order to be confident of having some that avoid their own high risk.

Within a few days of fertilization, all the thriving embryos will have a cell removed for genetic analysis. The whole genome sequencing will happen rapidly, as will
the computerized analysis of the resulting variations. This will lead to part of the process that will be not only the most time sensitive, but will require the most skilled labor. The prospective parents will have to decide, based on expert information provided to them by someone interpreting the embryos’ genomes, which one or two embryos to transfer. (Note that the easier and less expensive the process becomes, the more likely prospective parents will be to choose to transfer only one embryo, thus avoiding the risks of multiple births.)

Let us spare a moment to think about this process of choice. The prospective parents will be presented with genomic information on, say, 20 embryos. They would first be told which of the embryos are unlikely to be viable, through chromosomal errors or other genetic variations that are lethal during fetal development. For the remaining, say, 17 embryos, they will get information about five to ten thousand powerfully genetic diseases. In fact, they will probably only be told about a handful, or less, of these diseases, the few that, according to their genomes, some of the embryos would develop. Let’s say that eliminates five more embryos, as likely to have, for example, Huntington disease in one case and Tay-Sachs disease in four others.

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2 Huntington disease is normally transmitted in an autosomal dominant fashion. For an embryo to have the disease-related allele, one of the parents would have to carry it — and, on average, half the embryos would carry it. As an example of the complexity of genetics, though, Huntington disease is caused by an expanded triplet repeat. People with 37 or more CAG repeats in a particular location on the Huntingtin gene will get the disease; people with 36 or fewer will not. But sometimes a parent will create a gamete that has more repeats — the DNA copying machinery will have “stuttered” — so that a parent with 32 repeats might have some eggs or sperm with, say, 38 repeats. That would be the explanation in this hypothetical example.

3 Of course, if gene therapy becomes sufficiently effective, an embryo with a genetically powerful disease risk might be “cured” of that risk through gene therapy, either before transfer, in utero, or after birth. It is possible that parents might choose such an embryo for its other traits and bank on curative gene therapy, but that would presumably require that one embryo to be their only embryo with the other traits they desire.
These first steps – rejecting embryos that would not be viable at all as well as those with powerful genetic variations that would cause severe disease – would be the ones that are, effectively, determinative. We will assume that no one will want to transfer non-viable embryos or embryos doomed to a serious genetic disease. For the remaining 12 embryos, the prospective parents will get more information. First, they would get information on which autosomal recessive disease alleles each embryo carries – alleles that could not cause disease in the person that embryo might become, but that could cause disease to its offspring. Then, they would learn about each embryo’s less powerful health risks – say, a percentage chance, based on the genes (and not on any environmental factors) that the embryo would grow up to develop each of, say, 50 diseases.

They would also get cosmetic information for each of those 12 embryos – hair color, eye color, skin color, nose shape, hair type, likely height, male pattern baldness, early gray hair, and so on. They would be given some, probably weak, information about likely behavioral characteristics – this embryo will have a 65 percent chance of having above average intelligence, a 35 percent chance of having above average musical ability, a 45 percent of having above average mathematical ability, and a 75 percent chance of being better at sports requiring endurance rather than sports requiring power or quickness. Finally (or perhaps first), they will be told “boy” or “girl.” The results may look something like Table 1.

Table 1

Four non-viable embryos
One embryo with a Huntington disease allele
Three embryos that would have Tay-Sachs disease

Of the remaining 12 embryos:

**Carrier status**

<table>
<thead>
<tr>
<th>Embryo #</th>
<th>Cystic fibrosis (CF), Fanconi Anemia (FA), Maple sugar urine disease (MSU), Niemann-Pick (NP), Phenylketonuria (PKU), Tay-Sachs disease (TS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embryo 1</td>
<td></td>
</tr>
<tr>
<td>Embryo 2</td>
<td>FA, Hurler syndrome (HS), Krabbe disease (KRB), NP, SC, TS</td>
</tr>
<tr>
<td>Embryo 3</td>
<td>CF, HS, MSU, PKU, Sanfillipo disease (SFP), TS</td>
</tr>
<tr>
<td>Embryo 4</td>
<td>Hur, NP, SC, SFP</td>
</tr>
<tr>
<td>Embryo 5</td>
<td>CF, FA, Krb, NP, SC, SFP, TS</td>
</tr>
<tr>
<td>Embryo 6</td>
<td>FA, MSU, P, SC</td>
</tr>
<tr>
<td>Embryo 7</td>
<td>CF, MSU, PKU, SFP, TS</td>
</tr>
<tr>
<td>Embryo 8</td>
<td>FA, Hur, Krb, NP, PKU, SFP</td>
</tr>
<tr>
<td>Embryo 9</td>
<td>CF, FA, MSU, NP, SC, TS</td>
</tr>
<tr>
<td>Embryo 10</td>
<td>FA, Hur, NP, SC</td>
</tr>
<tr>
<td>Embryo 11</td>
<td>Hur, Krb, MSU, NP, PKU, TS</td>
</tr>
<tr>
<td>Embryo 12</td>
<td>CF, Krb, NP, PKU, SC</td>
</tr>
</tbody>
</table>

CF is cystic fibrosis
FA is Fanconi anemia
Hur is Hurler syndrome
Krb is Krabbe disease
MSU is Maple sugar urine disease
NP is Niemann-Pick
PKU is Phenylketonuria
SC is Sickle cell disease
SFP is Sanfillipo disease
TS is Tay-Sachs disease

**Sex**

<table>
<thead>
<tr>
<th>Embryo #</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>M</td>
<td>F</td>
<td>F</td>
<td>M</td>
</tr>
</tbody>
</table>

**Disease Risks**

Expressed as a percentile of general population risk

<table>
<thead>
<tr>
<th>Embryo #</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
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<tbody>
<tr>
<td>Heart Disease</td>
<td>60%</td>
<td>25%</td>
<td>35%</td>
<td>70%</td>
<td>45%</td>
<td>85%</td>
<td>40%</td>
<td>45%</td>
<td>65%</td>
<td>35%</td>
<td>85%</td>
<td>50%</td>
</tr>
<tr>
<td>Stroke</td>
<td>40%</td>
<td>55%</td>
<td>40%</td>
<td>55%</td>
<td>35%</td>
<td>65%</td>
<td>70%</td>
<td>45%</td>
<td>55%</td>
<td>45%</td>
<td>50%</td>
<td>55%</td>
</tr>
<tr>
<td>Asthma</td>
<td>80%</td>
<td>45%</td>
<td>55%</td>
<td>50%</td>
<td>50%</td>
<td>45%</td>
<td>60%</td>
<td>60%</td>
<td>45%</td>
<td>60%</td>
<td>85%</td>
<td>40%</td>
</tr>
<tr>
<td>Colon Cancer</td>
<td>55%</td>
<td>40%</td>
<td>60%</td>
<td>75%</td>
<td>45%</td>
<td>60%</td>
<td>45%</td>
<td>40%</td>
<td>80%</td>
<td>30%</td>
<td>20%</td>
<td>45%</td>
</tr>
</tbody>
</table>
Lung Cancer | 45% 50% 55% 40% 45% 50% 40% 45% 50% 45% 55% 45%
Breast Cancer | 20% N/A 30% N/A 15% N/A 45% N/A N/A 20% 40% N/A
Prostate Cancer | N/A 75% N/A 80% N/A 95% N/A 85% 75% N/A N/A 95%
Rheumatoid Arthritis | 70% 25% 65% 40% 50% 15% 80% 35% 45% 60% 70% 30%
Type 1 Diabetes | 20% 15% 10% 20% 15% 5% 10% 15% 20% 15% 10% 20%
Type 2 Diabetes | 65% 70% 50% 75% 80% 75% 65% 80% 65% 80% 75% 55%
Alzheimer Disease | 15% 45% 45% 90% 45% 15% 90% 15% 45% 45% 15% 90%
Schizophrenia | 50% 50% 45% 50% 40% 55% 50% 45% 55% 50% 50%
Bipolar Disorder | 65% 55% 40% 65% 70% 55% 65% 70% 65% 40% 50% 66%
Autism | 25% 35% 70% 45% 85% 40% 45% 65% 35% 85% 50% 65%

Cosmetic Traits
Brown (brn), Black (blk), Hazel (hzl), Straight (str), Curly (crl)
Skin color is based on a chart showing 100 different skin tones

<table>
<thead>
<tr>
<th>Hair color</th>
<th>brn</th>
<th>brn</th>
<th>blk</th>
<th>brn</th>
<th>blk</th>
<th>brn</th>
<th>brn</th>
<th>brn</th>
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<th>blk</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Eye color</td>
<td>brn</td>
<td>brn</td>
<td>hzl</td>
<td>brn</td>
<td>brn</td>
<td>hzl</td>
<td>brn</td>
<td>hzl</td>
<td>brn</td>
<td>brn</td>
<td>hzl</td>
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<tr>
<td>Skin color</td>
<td>#25</td>
<td>#27</td>
<td>#23</td>
<td>#32</td>
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<td>#34</td>
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<td>#27</td>
</tr>
<tr>
<td>Hair type</td>
<td>str</td>
<td>str</td>
<td>crl</td>
<td>str</td>
<td>crl</td>
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<td>str</td>
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</tr>
<tr>
<td>Male pattern baldness</td>
<td>N/A</td>
<td>no</td>
<td>N/A</td>
<td>yes</td>
<td>N/A</td>
<td>yes</td>
<td>N/A</td>
<td>no</td>
<td>yes</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Behavioral Traits
The first two are expressed as percentage probabilities; the last three are likely percentile ranking compared with the general population

| Above average IQ | 35% 70% 65% 45% 55% 25% 65% 60% 35% 50% 55% 40% |
| Top 10% IQ        | 5% 15% 15% 10% 10% 5% 15% 10% 5% 10% 10% 5%    |
| Athletic ability  | 65% 50% 70% 45% 40% 75% 60% 55% 80% 50% 40% 50% |
| Musical ability   | 30% 75% 45% 40% 25% 65% 75% 25% 50% 35% 50% 40% |
| Extroversion      | 50% 25% 45% 65% 35% 40% 45% 40% 60% 35% 65% 50% |

The prospective parents will get a print-out like this – though with far more traits described – and will likely have 24 hours or so to select which one or two embryos they want to transfer in this effort. They may also be asked to choose other embryos for freezing and possible future use, although depending on the cost of doing the Easy PGD procedure and the efficacy of embryo freezing (currently the success rate of IVF using
frozen embryos is lower than the success with fresh embryos, though it is not clear how big a role freezing plays in that outcome), it may make more sense just to go through the process again every time they want to try to establish a pregnancy. What kinds of help the prospective parents will need in making those decisions will be discussed in chapter 17.

Within a short time of the making the decision, the lucky embryo or embryos will be transferred into a uterus – of the woman in the heterosexual couple, in one of the women in a lesbian couple, of the single woman who wants to be a parent, or of a gestational surrogate. Within a few days testing will be able to tell whether or not the pregnancy has started, at which point Easy PGD may well be over and regular prenatal care begun. The “may well be over” comes from the possibility PGD’s error rate may still be high enough to require subsequent follow-up, probably through non-invasive prenatal diagnosis (NIPD) at about the fifth week of pregnancy.

About forty weeks after the embryonic transfer, if all has gone well, the prospective parents will no longer be “prospective.” At that point, they will begin the disconcerting but exciting challenge of learning the near-infinite number of the things about their new baby that Easy PGD did not warn them about.

That’s what Easy PGD would look like for prospective parents. What would it look like for society? That depends largely on how widely it is adopted, which in turn depends heavily, though not entirely, on its price.
That price should be, in effective terms, zero. That its price is zero does not mean Easy PGD will have no cost. It will require various human and technical inputs and those will cost money. One cost will be performing the skin biopsy in order to get cell samples to be transformed into iPSCs. A trained nurse could do that in a few minutes; let’s cost that out, in today’s dollars (not adjusting for inflation in the next 20 to 40 years) at $50. (Of course, if one could effectively use cells scraped by the donor from the inside of her cheek, that cost can be avoided.) The hardest cost to calculate is that of de-differentiating the donated cells into iPSCs and then re-differentiating them into eggs or sperm. Progress in more general use of stem cells is likely to have made that relatively mechanized and routine, but there will be costs. I will estimate, without a great deal of confidence, that this would cost about $1,000.

The PGD process will require a skilled professional to extract at least one cell from each embryo. Just the extraction seems likely to cost at least $50 per embryo. The actual genetic diagnosis and interpretation, however, should be very inexpensive that far into the future. The sequencing will be mechanized and the interpretation will be computerized. Call that another $50 per embryo. The most expensive part of the process will be the discussion of the results with the prospective parent. As discussed in chapter 17 below, that might be done in a variety of ways, including a completely automated process. A more likely alternative would include some automated return of results (and counseling), probably through internet-delivered videos, and some interaction, preferably face to face, with a trained professional. Call that another $500.
All in all, this adds up to $1550 per attempt, plus $100 per embryo. Assume a minimum attempt will create 20 embryos, though one could probably find at least one embryo or either sex without any serious disease risks by using only 10 embryos. At 20 embryos, the total cost would be about $3,500; at 10 embryos it would be about $2,500. Now add another 50 percent for overhead (including liability insurance) and the bottom line cost should be somewhere around $5,000 for 20 embryos or $3,750 for 10 embryos.

Of course, predicting the costs 20 to 40 years from now of procedures not yet invented seems almost the definition of a foolish task. Nevertheless, the exercise can provide some help. If the technologies develop as I expect, the cost seems unlikely to be more than twice as high as estimated and could easily be half as much. (The cost estimates are quite responsive to the estimated costs per embryo of extracting one cell and then of performing PGD on it.)

Assume, then, a cost around $5,000. Why would the price be effectively zero? Because at that cost the procedure should pay for itself for insurers and other health programs. One end result of Easy PGD should be fewer sick children, and, ultimately, healthier adults. At $5,000 per cycle, it would cost $500,000 to use Easy PGD in 100 pregnancy attempts. Assume that those 100 Easy PGD cycles yield 100 births. This would not, of course, be the result of 100 percent efficiency in Easy PGD pregnancies, but some of those pregnancies will be twins or (perhaps) other multiples and in other cases the prospective parents will use embryos from one Easy PGD attempt in several
different pregnancies through embryo freezing (or simultaneously through the use of surrogates).

Out of 100 live births, one would expect 2 of the babies to have, or rapidly to develop, serious health problems that could have predicted with genetic testing. Most of these children will have rare diseases, but 5,000 rare diseases spread over 4.3 million births a year produce a lot of tragedy. If the net present value of the cost of the health care that will be provided to those children were to be $250,000 each, the tests are, in effect, “free” to the health care system. And that is before counting the costs of the higher risks of later onset diseases that might be avoided, from cases of breast and colon cancer, to cases of sudden cardiac death, to cases of Alzheimer disease. The later the onset of the onset of the disease, the lower the net present value, but $1 million spent in long term care for an Alzheimer patient at age 70 would still have a nontrivial net present value. (It would work out to over $100,000 using a three percent discount rate.)

Of course, the “health care system” is not necessarily the same as any one insurer or government program that pays for health care. In a system with multiple health care payors, the one that pays for PGD would not necessarily be the one that benefits from the lower health care costs. Of course, much of the developed world has health coverage that comes from a single payor, or from closely integrated payors. Even in today’s United States, the health costs for an infant are likely to be paid by the same entity that pays for the pregnancy and deliver. (The most common payor for pregnancies, accounting for about 40 percent of all births in the United States, is Medicaid, the federal-state program
that pays for health care for the poor.) Predicting health care financing systems 20 to 40 years in the future seems, to me, even crazier than predicting the costs of not yet invented technologies; at any rate, it seems plausible that overall health care system costs will, in one way or another, be considered in deciding whether to cover Easy PGD.

And, of course, health coverage is not intended to make money or even to break even. We believe it is worthwhile to spend money to prevent and treat human suffering. Otherwise we would pay for no health care and have no health care costs. People “buy” health care – directly through out of pocket payments or private insurance, semi-directly by choosing to work for employers that provide health coverage, indirectly through government programs – because health care, and the anticipated decreases in suffering and increases in life span have value to them. In addition to – and ultimately much more important than – the financial costs avoided by Easy PGD would be the costs in human suffering for the people born with the diseases, as well as the families into which they are born. Those values should dwarf the financial costs, but if, in addition, the financial costs are negative – if Easy PGD in the long run saves the health coverage system more money than it costs – that will surely be a strong incentive to adopt it. And this holds true whether the health coverage is provided by private, for-profit insurers; private, non-profit insurers; or government programs. It may not be a perfect incentive – there may well have been cost-effective disease prevention efforts that insurers have not covered – but it will be a push toward subsidizing Easy PGD.
So, assume that the cost to patients is, thanks to health coverage, effectively zero or so low as to be a trivial consideration. How widely would Easy PGD be used? That is another difficult question.

Currently about 4.3 million children are born each year in the United States as a result of about 4.2 million pregnancies that end in “live births.” (Multiple births account for the differences). Roughly another million pregnancies end in abortions each year.

Women report that about 50 percent of births are the result of planned pregnancies. This could be seen as an upper bound for the market for Easy PGD. After all, unplanned pregnancies cannot use this process. On closer examination, though, that 50 percent number is not entirely fair. Another 30 percent of so of births are, though not planned, the result of a willingness to get pregnant. The woman may not have been affirmatively trying to have a child right now, but was not using contraception and was willing to have a child now if it happened. Only about 20 percent of births were the result of unwanted pregnancies. And, on the other end, about 1.5 percent of births are the result of IVF, the *ne plus ultra* of planned pregnancies.

We have a little, but only a little, data to help us guess to the likely choices of prospective parents who have the option of Easy PGD. We know that, in 2009, only about four percent of the 145,000 IVF cycles included PGD. We also know that somewhere under one percent of all U.S. pregnancies undergo amniocentesis or CVS.
But almost every pregnancy now, at least that where the pregnant woman receives any prenatal care, will use ultrasound to look for problems in fetal development.

Between these methods lies prenatal screening. These methods use blood draws from the pregnant woman to look for molecules that indicate a high or low risk of Down syndrome and of a series of non-genetic conditions called neural tube defects. This screening is usually done through two blood draws, one in the first trimester and one in the second, plus a second trimester ultrasound. For Down syndrome, they cannot presently completely rule in or rule out the existence of the condition – therefore, they are screening tests only, and not diagnostic tests. Fetuses shown to be at low risk through this screening have an extremely low chance of having Down syndrome and pregnant women, even older women who are at higher risk for a Down syndrome pregnancy, usually do not move on to actual genetic testing. Women whose pregnancies are shown to be at high risk still have, at most, about a 20 percent risk of having a Down syndrome fetus. Some of them choose to follow this up with amniocentesis or CVS; others, particularly those who would not choose to abort a fetus with Down syndrome, do not.

This kind of screening has been available, with increasingly good accuracy, for about 30 years. Overall, about ___ percent of American pregnancies receive any significant prenatal care. Of those pregnancies, about ___ percent use prenatal screening. We have most information about California. In 19__, the California legislature required every obstetrician to offer prenatal screening to every woman first presenting to the doctor at less than 20 weeks of pregnancy. The California statute requires that the test be
offered, not that it be accepted. The evidence from across California is limited, but tends to show that about 80 percent of pregnant women offered the screening test accept it. And note that these are all pregnancies where there is prenatal care, not just planned or "desired" pregnancies.

One might expect that woman who accept this prenatal screening for Down syndrome and neural tube defects, serious medical conditions for which no good cure exists, would be willing to use Easy PGD. But there are at least two barriers to that conclusion.

First, it is not clear that all the women who agree to prenatal screening actually know what they are accepting. The procedure requires them to sign a consent form, whose contents are mandated by the state, but pregnant women, like other patients, sign many forms and, on occasion, do not understand or even read them. The procedure just involves, in the first trimester, one more tube of blood to be drawn in one of the many blood draws that are part of prenatal care. In the second trimester, it requires another tube of blood, plus an ultrasound that the woman was almost certainly going to have anyway. Genetic counselors, who often have the task of explaining a high risk screening test result to a woman, report anecdotally that many of the women do not realize they had such a test, deny authorizing it, and say that had they known what it was, they would not have had it. We have no data on how many women respond that way; it seems to be a minority but not a tiny minority.
Second, the women who choose prenatal screening are already pregnant. Women need to choose Easy PGD before they become pregnant. And, unlike the prenatal screening test, Easy PGD will involve additional procedures (at least the skin biopsy) and additional doctor visits (both for the biopsy and to discuss the results). But there is more in play than just procedures. Becoming pregnant is important, and primal, and, I think even a man can confidently say, not always a matter of logic. Naturalness, romance, mystery, fate, and a variety of other emotional and cultural responses can be bound up in the process of becoming pregnant, or even of deciding to become pregnant – or deciding to be open to the possibility of becoming pregnant. Making a decision about tests for a pregnancy that has already started may well be quite different from making a decision about a pregnancy before becoming pregnant.

So, how to add this all up? Some prospective parents might not choose to use the technology as a result of religious, philosophical, ethical concerns – or less easily described personal and emotional responses. Presumably almost all parents who use IVF would be willing to use Easy PGD, if only to improve their chances of successful IVF. It also seems likely that most planned pregnancies would choose to use free, safe Easy PGD. Some may do it to avoid the most serious health risks, some may do it to select their baby’s sex, and some may do it for more traits. If Easy PGD is free, presumably many, though not all, of those planned pregnancies would begin with Easy PGD. Of the desired but unplanned pregnancies, some prospective parents will see enough advantages to PGD to push them over into the “planned category,” but others will not. And presumably some undesired pregnancies might be avoided and replaced with planned
pregnancies using PGD – but I suspect not many. Some babies will continue to be conceived in bed, in the back seats of cars, and under “Keep Off the Grass” signs; by people too young and impulsive to think about alternatives or by those who could, but don’t, think about them.

How many unplanned pregnancies will happen? It depends, on, among other things, just how deeply these new technologies affect how people live. If, in fact, you could make gametes safely, easily, and cheaply from iPSCs, people might make some very different choices about reproduction.

Dr. Carl Djerassi, one of the fathers of the oral contraceptive, argues that eventually people will be sterilized at puberty, either in a way that is reversible or with the storage of eggs and sperm in order to start a pregnancy later, when, and only when, planned. Easy PGD could, of course, fit right into Djerassi’s world – gametes from iPSCs would avoid the need for either reversible sterilization or storage of gametes. At least in the United States, his scenario seems culturally unlikely. I do suspect, though, that parents may have long-term contraceptives implanted in their teenage children, to be removed, or not, by the children when they become adults.

But what about adults? Would adults choose to be sterilized if they knew that they could always become parents through gametes made from iPSCs? “Sterilization” in that context would be nothing more than temporary, but highly effective, contraception, a process that prevents unwanted conception but does not interfere with subsequent
planned pregnancies. It might not be much better than existing methods of contraception for women (though it would avoid any perceived or real health risks from oral contraceptive or IUDs), but it would really provide, for the first time, powerfully effective male contraception. Cheap, easy, and safe production of gametes from iPSCs, with or without PGD, might lead to social changes that greatly reduced unplanned pregnancies. Or not.

Finally, if it works well, the use of Easy PGD will undoubtedly increase with time. Some people love to be early adopters – of new computers, of new cell phones, of new medical technologies, and of new sources of genetic information. Not everyone stood in line to get the first generation iPhone or iPad, just as not everyone signs up for direct-to-consumer genetic testing. When it comes to medical technologies, most people – and most doctors – prefer to be neither the first nor the last to adopt something new.

My own guess is that once Easy PGD has been available clinically for 10 years or so, somewhere between 50 and 70 percent of pregnancies in the U.S. will have been started using it. Most of the people who currently plan their pregnancies will want it, about half of those who have desired but unplanned pregnancies will switch to planning in order to use Easy PGD, and a few people with undesired pregnancies will instead have desired Easy PGD pregnancies. If the technology continues to be, and to seem, effective, that percentage should rise over time, but, without coercive measures or major social changes in controlling reproductive capability, it is unlikely ever to approach 100 percent. Some people will always refuse the technology, for reasons of principle or personality.
And some pregnancies will always be unplanned accidents. But, in the long run, I could imagine 90 percent U.S. pregnancies being the result of Easy PGD.

These percentages, of course, will doubtless vary in other countries, with other cultures, health care systems, and economies. Some will use it less; some may well use it more. The implications of these differences in the use of Easy PGD raise important social implications, discussed in Chapter 14.

**Alternative Futures**

The science, and its translation into clinical practice, could lead to several variations in this future.

The biggest showstopper would be the discovery of some irremediable safety problem with IVF. For all we know, every person conceived through IVF could drop dead at age 35. The oldest such person, Louise Brown, was born in 1978. I will discuss the safety issues around IVF, with or without Easy PGD, in chapter 12. Major issues seem unlikely to arise, but they cannot be considered impossible. And certainly the discovery of smaller but non-trivial risks is entirely possible. In a world where IVF had serious and unpreventable risks, not only would Easy PGD not be used but IVF would be used much less frequently, if at all.
In another one of those futures, the safe and effective derivation of oocytes from stem cells proves to be impossible. In that case, Easy PGD might still exist for some people, but in a much less popular form, one that is not nearly as “easy.” Women who want to use PGD but who want to avoid the arduous process of preparing for egg harvest may choose extraction of immature oocytes followed by in vitro maturation. Both of these technologies are currently possible and presumably will improve in the future.

But these immature oocytes will still need to be extracted. The extraction will not require the hormone injections, with all their side effects, but will still require an invasive surgical procedure. Granted, it would be a laparoscopic surgery, almost the same as the actual harvesting procedure currently used in egg harvest. Women may be able to choose to do it only once in their (reproductive) lives, extracting and freezing a slice of ovarian tissue, to be thawed and used as necessary. Or they may opt for a new retrieval with every attempt at pregnancy. These procedures would probably be more expensive than egg derivation, if only because they require more skilled labor for the surgery. And they will necessarily be more invasive and uncomfortable for the woman, though not as uncomfortable as current egg harvest methods. I would expect, in this future, for PGD to be used more widely than it is today, but still probably a minority decision, and definitely less common than in an Easy PGD world.

Note, though, that in vitro maturation does rule out some applications of Easy PGD. It would not be available to provide gametes for people who do not have their own, the most medically, and politically, compelling use of Easy PGD. They would have
to continue to use donor gametes, to adopt, or to be childless. This future also rules out making sperm from women or eggs from men (or both from one person). Avoiding the possibility of “uniparents” may cause little concern, but preventing prospective parents who are gay or lesbian from having “children of their own” would be a substantial loss to them.

Another possibility is that deriving eggs proves to be possible, but not through iPSCs. It might still be the case that the process for turning skin cells (or other cells) into embryonic-like pluripotent cells will never be made safe. This seems unlikely, in part because of the great interest throughout medicine (and not just in reproduction) in making iPSCs. But there may turn out to be insurmountable problems. Then what?

If eggs (and sperm) can only be derived from embryonic stem cells, the process may still be used by people who do not make their own gametes. It would be much less widely popular than Easy PGD because it will not give prospective parents a “child of their own” though they may be able to choose among a wide range of different hESC lines to find one that has a genome “closest” to their own.

Stem cells from somatic cell nuclear transfer (“cloned” stem cells) could provide yet another option, either through the Columbia “triploid” process or in a more straightforward, though as yet unknown. It is not clear how popular this would prove, if effective. It has the disadvantage of requiring some eggs to start the process. If they are not the prospective mother’s own eggs, it raises the possibility of problems from an
incompatibility between the prospective mother’s nucleus and the egg donor’s cytoplasm. It is hard to see that SCNT would ever have any advantages over a safe and effective version of using iPSCs to make gametes – at the very least it requires an additional step of replacing the donor egg’s embryo – but, like iPSC but unlike hESC, it would give people gametes made from their own genome.

The other uncertainties are economic and political. It is possible that Easy PGD will not be as inexpensive as I expect. In that case, its use may be limited, especially if political concerns about the procedure prevent it from being subsidized, either by governments or by insurers. The cost of the PGD will almost certainly be quite low, but the cost of making safe iPSCs from individuals is unknown at this time. Even more unknown is the cost of deriving gametes from stem cells. With IVF currently costing $15,000 and more, even if Easy PGD costs $15,000 instead of $1,000, it will have some market, but that market is not likely to be big enough to be revolutionary. Of course, that conclusion depends not only on issues of cost, insurance, and subsidy, but also of economic growth and income distribution. If per capita income were to grow at an average rate of three percent per year, in 30 years it would be 2.4 times as high as it is today. With family incomes 240% higher, even $15,000 would be affordable for many more people.

Finally, political actions may change the future. I laid out in Chapter 11 some of the reasons I believe that political factors are not likely to limit Easy PGD substantially, at least in the United States, though they may lead to regulations or bans of some extreme
uses. But political sentiments are volatile. The United States may end up enacting, on a federal level or, perhaps more likely, in individual states, prohibitions or restrictions on Easy PGD based not on safety and efficacy, but on ethical and moral concerns. The next section of the book explores those ethical and moral concerns, as well as a few pragmatic issues Easy PGD would raise. You can, and should, judge for yourself whether those concerns will, or should, lead to the significant restrictions on Easy PGD. Empowering my readers to make an intelligent and informed decision about Easy PGD is the reason I wrote this book. So, let’s look at the implications of Easy PGD.
Section Three

Implications

Miranda: “O, Brave new world that has such people in’t!”

Prospero: “’Tis new to thee.”

Shakespeare, The Tempest

This section explores the likely implications of Easy PGD. It is mainly looking at risks, disadvantages, and other “problems” with Easy PGD. Some of these problems are speculative and may never come to pass, others may subject to mitigation by wise policy, but others will be real and unchangeable. I have grouped the risks into six chapters, looking at safety, family relationships, equality, coercion, naturalness, and a last category, which I call “legal and practical” (but which might as easily be called “other”).

Some of these issues have been explored at great length and depth, since well before the technologies for even primitive prenatal genetic testing was available. Aldous Huxley’s Brave New World, published in 1932, contained some of these critiques; so did H.G. Wells’s The Time Machine, published in 1895, and, in a very broad sense, Mary Shelley’s Frankenstein, or the Modern Prometheus, published in 1816. More recently, many non-fiction books and articles have been devoted more specifically to the hazards of human genetic selection, motivated not just by earlier fiction but by the all too real atrocities committed by Germany during the Nazi regime in the name of eugenics. (Germany was, of course, not alone in its misdeeds – the Nazi law on eugenics was
modeled on the statute in force in my own beloved California – but the Nazis were unique in the lengths to which they took the idea.)

I will not discuss all, or even much, of that pre-existing literature, or even the best examples of it. Life is short and the books stack too high. Much of what I have to say about the implications is, at best, my own variations on the insights of earlier authors, particularly with respect to family relationships, equality, and naturalness. My contribution there lies in applying the somewhat abstract concerns raised by others to a concrete setting, and a setting that I hope I have convinced you is not only one plausible future but the most likely future scenario for widespread prenatal genetic selection. American lawyers like to apply principles to concrete cases, rich with facts and context. That approach has strengths and weaknesses, but, for better or for worse, it is my approach for the rest of this section.

Before turning to those costs and risks, I do need to say a word on the benefits. It may seem a bit unfair to have six chapters of risks, disadvantages, and problems, and only the next three paragraphs to discuss the benefits, but the cost/benefit scales do not weigh chapters, pages, or words. The benefits of Easy PGD are simple to state, if hard to quantify, and many of them are implicit in the earlier chapters of this work. I see three.

The first benefit is a decrease in the amount of human suffering caused by genetic disease. Far fewer babies will be born with disabling and fatal genetic conditions. If we set that amount at about 2 percent of current births and assume that easy PGD prevents
even only half of those births, that would “prevent” the suffering of about 40,000 children – and their parents and other family members – each year in the United States alone. And it would prevent the suffering of those children later in life from diseases with a strong genetic component but with a later and perhaps a less certain onset. Of course, it would prevent that suffering by preventing the children, not by preventing the disease in those children, but each child not born with a terrible genetic disease would be replaced by a child born without those diseases.

The second benefit is a (slightly) closer match between the children parents want and the children parents get. This closer congruence must not be overestimated. I am a parent of two children who have regularly surprised me and, I am sure, will continue to do so throughout our mutual lives. Very few of those surprises could have been prevented by Easy PGD because very few of the surprising details of their lives could be predicted strongly (if at all) by their genetic variations. If parents think they want children who will grow up to be tall, with dark eyes, and a greater than average chance of being good musicians, getting such children should be counted as a benefit. One might question whether parents (and their children) really are better off if the surprises from children are somewhat diminished – this will be a major topic of discussion in chapter 13 – but if at least some parents think they will be, it is hard to second-guess their implemented perceptions of their own preferences.

The third benefit is more subtle, and negative in nature. If Easy PGD can be developed as a safe and effective technology, the freedom to use it – or, more accurately,
the freedom from prohibitions on its use – should be counted by itself as a benefit, at least by people who have a preference for freedom. Freedom to choose, particularly in health care, is often infringed and, I believe, often for very good reasons. But infringing freedom is always a cost, even when that cost is far outweighed by the benefits.

Those are the three potential benefits of PGD. One could spin them out in more detail – a decline in genetic disease, for example, is also a decline in health care expenditures for those genetic diseases – but those three are it. They may seem frail reeds against the storms of the next six chapters, but, at the end, we will weigh those benefits against the costs. In light of that balance, as I see it, I suggest, in a final chapter, what I think should be done. And I will ask each of you to work the scales yourself and to decide, from your perspective, what is to be done. But to do that, you need to learn about the costs. So let us begin.