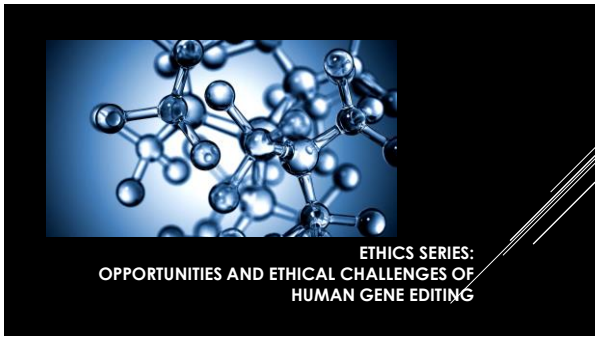
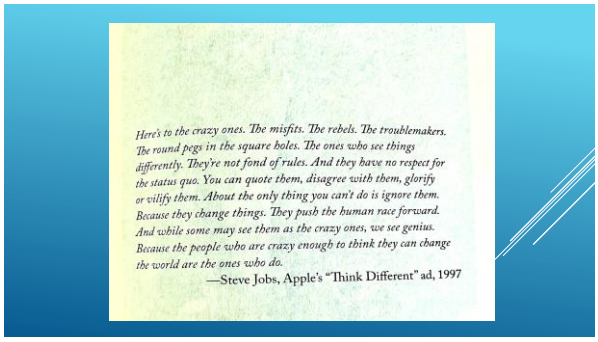
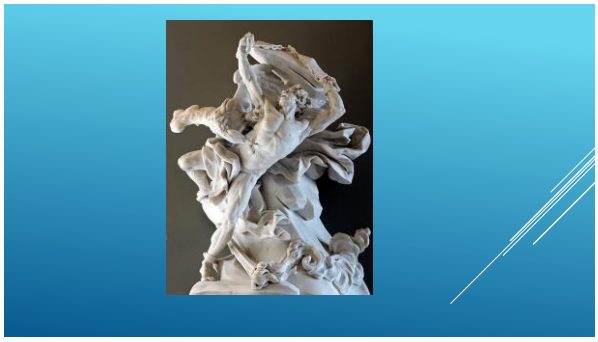

ETHICS SERIES:
OPPORTUNITIES AND ETHICAL CHALLENGES OF
HUMAN GENE EDITING

1


Here's to the crazy ones. The misfits. The rebels. The troublemakers.
The round pegs in the square holes. The ones who see things
differently. They're not fond of rules. And they have no respect for
the status quo. You can quote them, disagree with them, glorify
or vilify them. About the only thing you can't do is ignore them.
Because they change things. They push the human race forward.
And while some may see them as the crazy ones, we see genius.
Because the people who are crazy enough to think they can change
the world are the ones who do.
—Steve Jobs, Apple's "Think Different" ad, 1997

2



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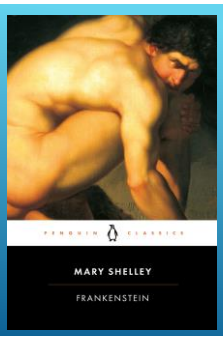

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REVOLUTIONS

- First half of 20th century: Physics (Einstein) – Led to the atomic bomb.
- Second half of 2oth century- Information technology (Jobs, DARPA) All information can be encoded in binary digits- Microchips, computers, internet
- 21st century Life sciences revolution

5

" Was the world ready for the new step forward? Certainly it will change the world. You have to make laws to fit it and if plain people do not understand and control it, who would?

James Agee "Atomic Age", *Time*, August 20,1945

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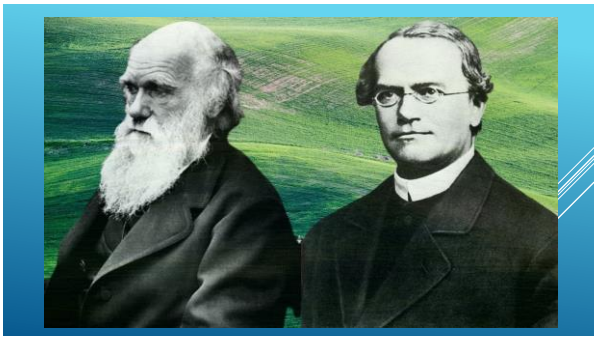

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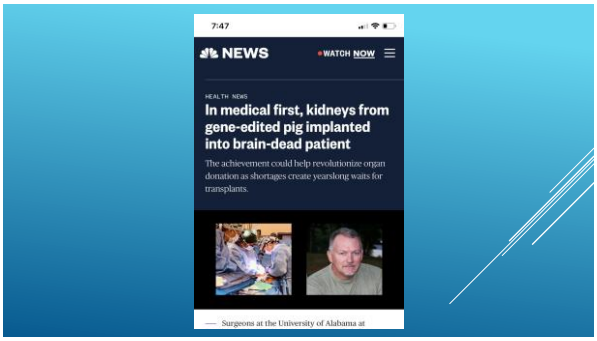
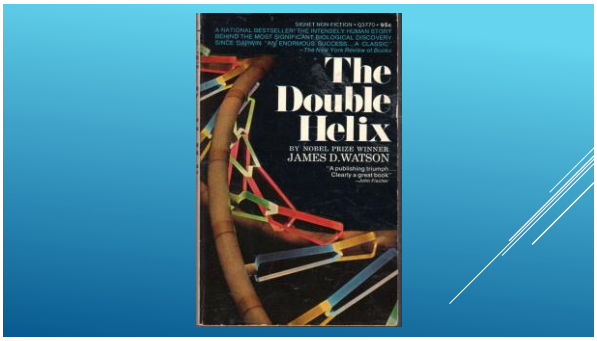

7:47
NEWS
WATCH NOW
HEALTH NEWS
In medical first, kidneys from gene-edited pig implanted into brain-dead patient
The achievement could help revolutionize organ donation as shortages create yearslong waits for transplants.
Surgeons at the University of Alabama at

8


The Double Helix
BY NOBEL PRIZE WINNER
JAMES D. WATSON

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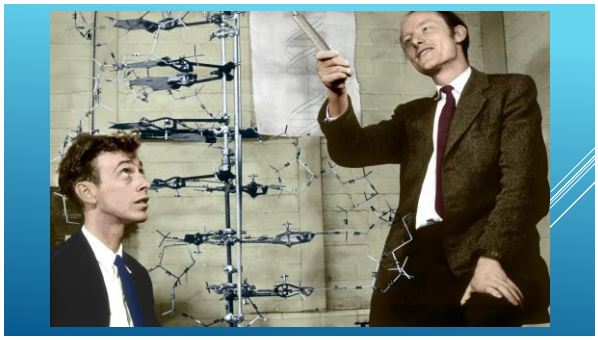

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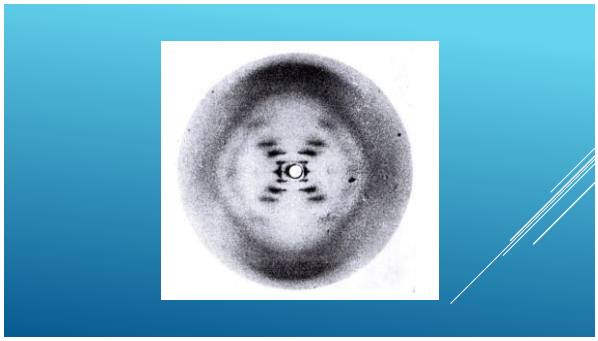

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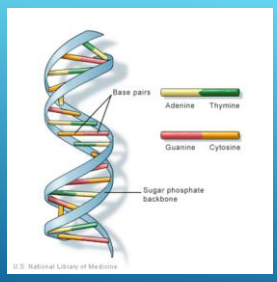

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- Structure of DNA published in 1953 (975 word paper typed by Watson's sister)
- Nobel prize 1962 Watson Crick Wilkins
- Rosalind franklin died in 1958 of ovarian cancer, likely as a result of exposure to radiation (like madame Curie)

INSTRUCTIONS FOR BUILDING EVERY CELL IN EVERY FORM OF LIFE WERE PRESENT IN FOUR-LETTER SEQUENCES

15

HUMAN GENOME PR0JECT

- 1986- Establish the sequence of 3.2 billion base pairs on human DNA
- Map more than 22,000 genes
- Found 41000 disease-causing mutations
- No cures
- Completed in 2021 T2T (Eric Lander)
- Bill Clinton " Today we are learning the language in which God created life"

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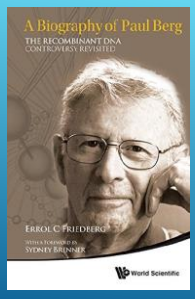

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RECOMBINANT DNA

- Paul Berg Stanford, (Nobel 1980)
- Splice pieces of DNA from different organisms to form hybrids
- Stanley Cohen, Herbert Boyer (Stanford)

  Discovered enzyme to make hybrids very efficiently and then be cloned to make millions of identical copies of a piece of DNA and introduce it into E.coli
- Birth of biotechnology **Genentech**
- Synthetic insulin - 8,000 lbs of pancreas from 23,000 cows and pigs needed to make 1 lb of insulin.

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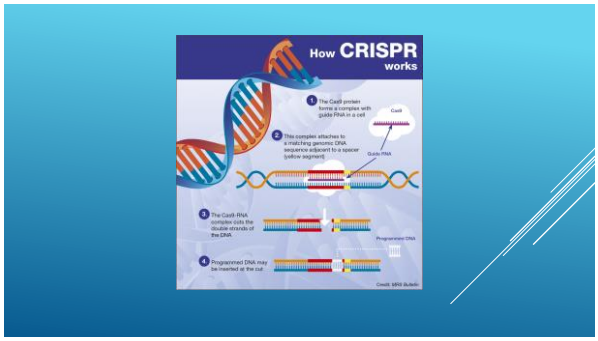

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CRISPR

- CRISPR paper published in *Science* in 2012
- Described the CRISPR Cas9 mechanism in vitro
- Suggested it could be programmed to become a gene editing tool
- There were many other collaborators and competitors that contributed
- Doudna " healthy rivalries have fueled many of humankind discoveries"
- How to get CRISPR into human cells?
- Within 6 months five teams Doudna, Church, Zhang, Kim, Joung had solved the problem.

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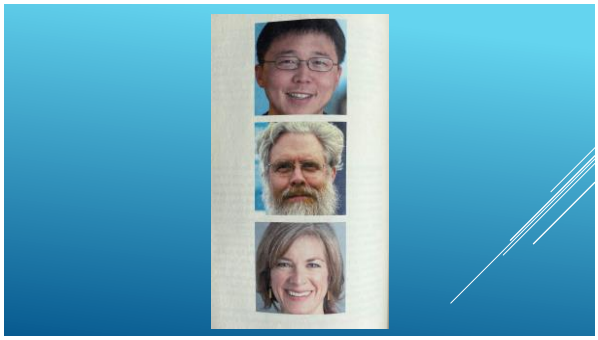

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CRISPR

- By 2020 it is possible to make single strand cuts , single base edits and insertion of long sequences of bases or base pairs
- Process is quick and efficient, reproducible
- Cut and paste, just like word processing

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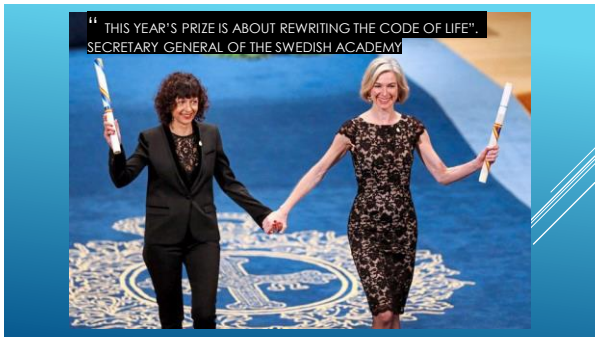

27

GENE THERAPIES

- First trial
- 15 years after Berg" discovery of recombinant DNA
- 1990 4 year old female with immune deficiency. T cells removed from her body were given the faulty gene
- T cells reintroduced into her body
- Dramatic improvement leading to a normal life

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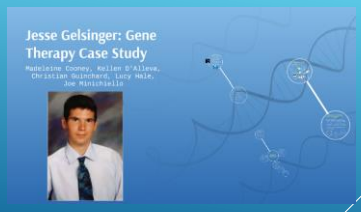

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PRE-IMPLANTATION GENETIC DIAGNOSIS

- In vitro fertilization
- First test tube baby, Louise Brown born in 1978
- 1990 pre-implantation genetic diagnosis
- Genetic testing of embryos to choose the most desirable qualities of the embryo to be implanted
- Allows parents to choose sex
- Tests for Huntington's disease, Tay Sachs, SCD, Down's syndrome (2/3 pregnancy termination in the US)

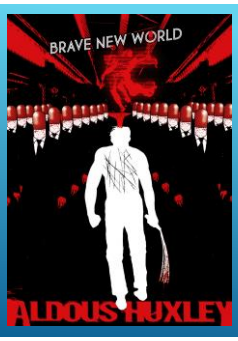
30

31

GATTACA

- Advertised in newspapers. At Gattacca it is now possible to engineer your offspring. "Children Made to Order" clinic
- Gender,stature, eye color, skin color, weight, addictive succeptibility, criminal aggressive tendencies, musical ability, athleticism and intellect
- None of the above
- For religious or other reasons you may have reservations about genetically engineering your child. We respectfully invite you to reconsider. From where we sit the human race could use a little improving
- In two days 50,0000 calls. The studio did not keep track of the choices.

32



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PRE-IMPLANTATION DIAGNOSIS

2019 New Jersey start-up

Genomic Prediction

IVF clinics send samples of prospective babies to be DNA sequenced to come up with statistical estimate of chances of developing a list of conditions (SCD,CF, diabetes, heart risk, hypertension, intellectual disability, height) for parents to choose which embryo to implant.

34

GENE EDITS

SOMATIC:

In vivo

Ex vivo

GERMLINE:

Changes are done in the DNA of human eggs or sperm or early-stage embryos that every cell in the resulting children and all of their descendants will carry

35

GERMLINE EDITS

CURES

SCD, blindness, Huntington's, thalassemia, cancer.

By 2020 there were 20 clinical trials using CRISPR to treat diseases.

PREVENTION

P53 (cancer), PCSK9 (heart disease), CCR5 (HIV) , APOE4 (Alzheimer's)

ENHANCEMENTS

Suppressing MSTS gene has allowed researchers to create "mighty mice", mutation of CDKNIC gene severely curtails size

Absolute: beneficial to all (increased intelligence, viral resistance)

Positional: Only benefit the individual

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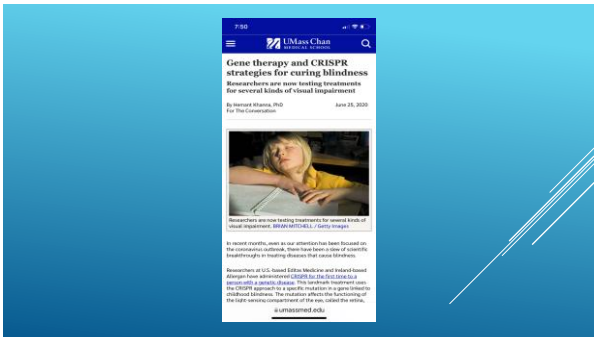

38

OPPORTUNITIES

- Used to develop vaccines Moderna (48 hours, 38 days, nanoparticles)
- Home Covid tests
- CRISPR based tests can detect up to 169 viruses at a time.
- Cas13 chops viruses in little pieces in vitro, decreasing viral loads up to 90%
- Problem has been finding a delivery system; the small size of the viral vectors limit the types of proteins and the size of the CRISPR RNA guides that are deliverable. They can be programmed to target "essential sequences" of the viruses so that they cannot easily be evaded by mutation

39

DARPA

- Defense Advanced Projects Agency
- DARPANET
- 2016 James Clapper US Director of National Intelligence "Worldwide Threat Assessment" Genome editing potential weapon of mass destruction
- Feared that a mad scientist could create a microbe that could destroy the planet.
- Supported research to create anti-CRISPR
- Use CRISPR to protect humans from nuclear radiation
- Vladimir Putin 2017 youth festival. CRISPR to create soldiers that could fight without pain, fear, mercy or compassion

40

41

ETHICS

42

QUOTES

- 1970 Bentley Glass President AAAS " The right that must become paramount is the right of every child to be born with a sound physical and mental constitution"
- 1974 Joseph Fletcher U. Of Virginia "The Ethics of Genetic Control" "" Producing children by sexual roulette without pre-conceptive and uterine control, simply taking pot luck is irresponsible now that we can be genetically selective".
- Robert Sinsheimer "Soon we shall have the power to consciously alter our inheritance, our very nature"
- James Watson " I was for researchers doing whatever they wanted"
- **Decisions about genetic future would be up to individual choice giving life to a new form of eugenics.**

43

QUOTES

- Paul Ramsey (Princeton) Professor of Christian Ethics. "Fabricated Man: The Ethics of Genetic Control" " Men ought not to play god before they learn to be men"
- Jeremy Rifkin (social theorist) "Who Should Play God?" "Once all this could be dismissed as science fiction, the mad ravings of a Dr. Frankenstein. No more, we are not in the Brave New World yet, but we are well along the road".

44

PRESIDENTIAL COMMISSION

- 1982 Jimmy Carter, National Council of Churches, Synagogue Council of America, US Catholic Conference letter: "We are moving into an area of fundamental danger triggered by the rapid growth of genetic engineering"
- The decisions should not be left up to scientists.
- " There will always be those who believe it appropriate to 'correct' our mental and social structures by genetic means. This becomes more dangerous when the basic tools to do so are finally at hand. Those who play God will be tempted as never before".
- "Splicing Life" presidential commission report
  - Called for further dialogue and societal consensus
  - Genetic engineering could increase and genetically encode inequity
  - Increased corporate involvement affects credibility and motivations of the scientists

45

UCLA 1998

- "Engineering the Human Germline"
- French Anderson- Distinction between treating diseases (moral) and genetic enhancements (inmoral)
- Watson-" If we could make better humans by knowing how to add genes why shouldn't we do it? It seems obvious that germline therapy will be much more successful than somatic cell edits. If we wait for the success of somatic therapy we will wait until the sun burns out… the biggest ethical problem we have is not using our knowledge and not having the guts to go ahead and help someone".

46

UCLA 1998

- Lee Silver (Princeton biologist) "Remaking Eden"
- " **Reprogenetics**" Use of genetics to determine which genes a child should inherit
- Framed the issue as one of individual freedom and liberty in a market-based consumer society
- Why , if parents can buy environmental advantages for their children can they not buy genetic advantages?
- Gregory Stock (organizer of the meeting)"Redesigning Humans: Our inevitable Genetic Future"

47

COUNCIL OF OVIEDO (SPAIN)

1997- Barred genetic genetic engineering in humans except for "preventive, diagnostic and therapeutic reasons and only where it does not aim to change the genetic make up of a person's descendants"

29 European countries incorporated these recommendations into their laws.

48

KASS REPORT

- Leon Kass, 1971 "*Science*" Germline gene editing would convert human reproduction into manufacture.
- George W. Bush 2002- Kass commission
- Kass Report- "Beyond Therapy" 310 pages
- Warned of using technology beyond treating diseases to enhance human capabilities.
- Discussed what it means to be human, pursue happiness, respect nature's gifts and accept the given.

49

NAPA 2015 CONFERENCE

- **Questions:**
- Up to the parents?
- Individual liberty?
- Up to society and the government?
- Would abandoning the random natural lottery undermine our sense of moral **empathy**?
- If the technology was there to make healthier babies would it be ethically wrong not to use it?
- Would we be decreasing **diversity**?
- Social justice and **equity**. Would only the wealthy have access?
- **Conclusions:**
  - Still too early to safely perform germline editing; someday it will happen, but guidelines are needed.
  - Somatic editing is a good thing that can lead to beneficial drugs and treatments.

50

2018 BRITAIN NUFFIELD COUNCIL

" Genome editing has the potential to give rise to transformative technologies in the field of human reproduction. So long as inheritable genome editing interventions are consistent with the welfare of the future person and with social justice and solidarity, they do not contravene any moral prohibition".

51

REGULATIONS

- Obama administration
- FDA barred from reviewing any treatment " in which a human embryo is intentionally created or modified to include a heritable modification".
- NIH- Would not fund any use of gene editing technologies in human embryos.
- 2003 China prohibited genetic manipulation of human gametes, zygotes and embryos for reproductive purposes.

52

53

GERMLINE EDITS

- 2015- germline edits in 86 non-viable embryos in China cutting out a gene that causes thalassemia
- He Jiankui edited the CCR5 gene (decreases the susceptibility to HIV) in mice, monkeys and non-viable human embryos
- 1.25 million HIV positive persons in China
- Widespread social ostracism
- Got IRB approval and videotaped informed consents
- Spring of 2018 implanted twin embryos with CCR5 edits

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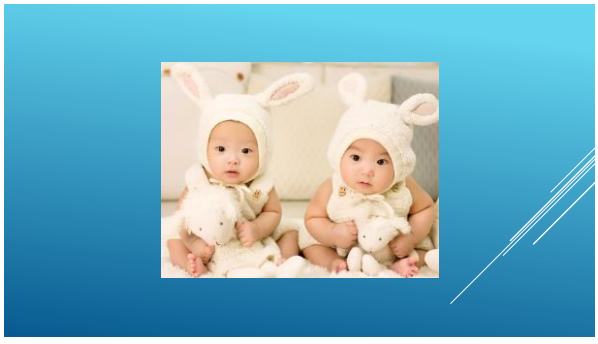

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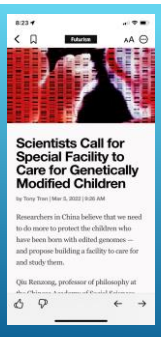
GERMLINE EDITING

- Global outcry- Naïve, reckless, disturbing, grandstanding act, irresponsible
- Lulu, only one of two chromosomes was modified, there were some off target edits, both embryos had been mosaics
- Sentenced to 3 years in prison, $430,000 fine, banned for life for working in reproductive science.
- Doudna- " The question is not if this is going to happen again, but when and how"

58


Scientists Call for Special Facility to Care for Genetically Modified Children

Researchers in China believe that we need to do more to protect the children who have been born with edited genomes -- and propose building a facility to care for and study them.

59

QUESTIONS

- Is there inherent goodness in nature?
- Is there a virtue from accepting what has been gifted to us?
- Does **empathy** depend on believing that by the grace of god, or randomness of natural lottery we could have been born with a different set of endowments?
- Will the emphasis on **personal liberty** turn the most fundamental aspects of human nature into consumer choices at the genetic supermarket?
- Should there be **societal consensus**?
- Should the rich be able to buy the best genes?
- Why would we not seize the opportunity to rid our species from dangerous diseases and enhance the capabilities of our children?

60

61

DISABILITIES

- How can we distinguish traits that are true disabilities (deafness, blindness) and ones that are disabilities because society is not good at adapting for them?
- To what extent are they truly disabling and to what extent are they due to our social construct and prejudices?
- Jory Fleming "How to be Human"- If gene editing were used to remove autism… "you'd be removing an aspect of human experience, but for what benefit exactly? Should society change to recognize the benefits of autism instead of just the challenges? Certainly my experience has been very challenging, but also rewarding".

62

ENHANCEMENTS

Suppressing MTS genes has allowed researchers to create "mighty mice".

Mutations of the CDNKNIC gene severely curtails size.

"Typical species functioning"

Enhancing genes for NDMA receptors could prevent memory loss in old age, could improve memory in younger people.

The new world- Light skinned, tall, attractive, athletic smart , emotionally stable. Is this truly what we want or desirable?

63

WHO SHOULD DECIDE?

- Individual rights, personal liberty, personal choice vs. justice and morality through the lens of what is good for society and for the species.
- Maximize individual liberty, minimize regulations intrusions by the state.
- Promote the common good, create benefits for all society minimize the harm, restrict selfish behaviors that might harm the community and the planet.
- The danger of genetic technology might not be too much government control, instead **too much individualized control** (libertarian eugenics)based on free choice and marketed consumerism.

64

WHO SHOULD DECIDE?

- Steven Pinker – "The Better Angels Of Our Nature"

Op-ed at the Boston Globe- " The primary goal of today's bioethics can be summarized in one sentence 'Get out of the way!' The last thing we need is a lobby of social ethicists. Don't get bogged down in red tape, moratoria based on principles such as dignity, sacredness, or social justice.'

65

INEQUITY

- Gene editing could exacerbate inequality and even **permanently encode it in our species**.
- We already accept inequality (better housing, nutrition, private school, coaches, SAT tutors, access to healthcare) based on birth and parental choices, but allowing parents to buy better genes would be a quantum leap in inequality.
- Basic premise of democracy is equal opportunity for all.
- "All men are created equal"?

66

INEQUITY

- Eric Sonthheimer-"In a world in which there are people who don't get access to eyeglasses it is hard to imagine how we will find a way to have equal access to gene enhancements. Imagine what it will do to our species."

67

68

The Moral Questions

If scientists don't play God, who will?
—James Watson, to Britain's Parliamentary and Scientific Committee, May 16, 2000

69

PLAYING GOD

- Francis Collins- " Evolution has been working towards optimizing the human genome for 3.85 billion years. Do we really think a small group of human genome tinkerers could do better without all sorts of unintended consequences?"
- Fen Zhang- "There is a blurry line between fixing abnormalities and making enhancements . What is wrong with making enhancements? I just don't like it. It's messing with nature and from a longer term population perspective you may be reducing diversity."
- Michael Sandel (Harvard Psychologist)- If we rig the natural lottery we will be less likely to view our traits as gifts that we accept, thus undermining empathy.

70

PLAYING GOD

- For all history humans (and every other species) have been battling rather than accepting nature's poisoned offerings. Evolution's primary guide is reproductive fitness, what traits are adaptative and give a species a better chance to survive.
- Jennifer Doudna- "Some day we may consider it unethical not to use germline editing to alleviate human suffering. As long as we are correcting genetic mutations, restoring the 'normal' version of the gene we are likely to be on the safe side."

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DIVERSITY

- Without gates or flags in the free market we would choose elimination of diseases, attractiveness, intelligence, athleticism and go barrelling at uncontrollable speed taking society into a lack of diversity and the human genome with it.
- Less deviation from the norm
- Less edge creativity
- Diversity is not only good for society, but also for our species, randomness in the gene pool has been shown to strengthen species and add resilience.
- **Diversity** conflicts with **individual choice**.
- What moral right do we have to require another family to forgo genetic intervention simply for the sake of adding to the diversity of society?

73

FUNDAMENTAL QUESTIONS

The question of engineering away mood disorders gets to an even more fundamental question: **What is the purpose of life?** Is it happiness, contentment, lack of pain or bad moods (think Soma).

Should the goal to be for people to flourish by using their talents and traits in a clearly fulfilling way?

This entails effort, sacrifice, pain, mental and physical discomfort, contributions to our community, society and civilization.

74

GENIUS AND MADNESS

- Challenges and so-called disabilities often build character, teach acceptance, install resiliency and may even be correlated with creativity.
- Miles Davis SCD, FDR polio, Beethoven deafness
- Genes for schizophrenia, bipolar disease and major depression have not bee identified yet.
- What if could edit out mental illness?
- **Schizophrenia**- Van Gogh, John Nash
- **Bipolar disorder**- Hemingway, Graham green, Gustav Mahler, Franz Schubert, Silvia Plath, Edgar Allan Poe
- **Major depression**- Thousands of creative artists- Robin Williams, David Foster Wallace, Yukio Mishima

75

Walter Isaacson- As with many other species this new capability may or may not be adaptative and may even lead the species to a path of extinction. As our guide, therefore we not only need scientists, but also humanists.

Carl Sagan- "Extinction is the rule, survival is the exception."

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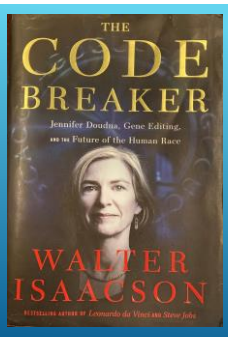

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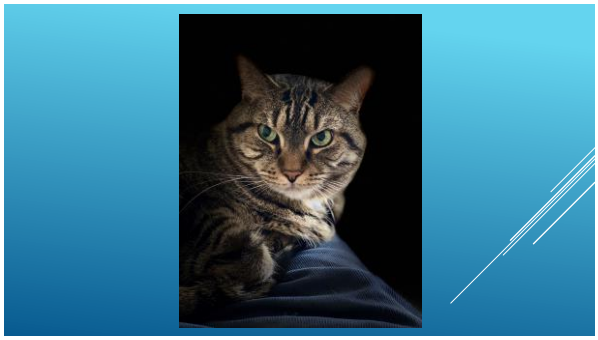

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