Harvard Medical School (HMS) Center for Bioethics
Ethics and Genomics
Winter 2025

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Course Overview:
Genomics play a critically important role in today's medical practice. More broadly, genetic information shape's individual identity, family relationships, community-identity and social practices. From predictive genetic testing, through issues surrounding genetic-relatedness, to direct-to-consumer 'recreational genomics' such as ancestry testing – genomics seems to be everywhere. Emerging genomics technologies, such as gene editing and three-parent IVF (in-vitro fertilization), are receiving ample media and academic attention, soliciting opposing reactions, from hyped enthusiasm to fears about a eugenic future. This class will cover the science, the ethical debates and the main policy approaches to well-established and emerging genomics technologies.

Evaluation:

%	What
20	Active and respectful participation in class discussions, including listening and responding to peers.
10	Response to a reading: short informal presentation (no slides) reacting to one of the readings assigned in the syllabus. The response can be a clarification, a critique, an argument in support, an application to a case, and more.
20	Gattaca film critique based on readings and class discussions. 800 words max. – see instructions at the end of this document
10	Outline of final paper: title, research question, main argument, outline in bullet points. 1 page max.
40	Final paper: a commentary on a topic of your choice, 1200 words max.

Expectations:
For each class meeting we expect you to have:
- done the readings
- prepared a question for each speaker (usually Dr. Holm and Dr. Ravitsky, but occasionally a guest speaker)

"Additional Readings" are not required, so read based on your interests as your time allows.
All readings will be accessible through Canvas.

Read for fun:
- Huxley. 1932. Brave New World. https://en.wikipedia.org/wiki/Brave_New_World
- Picoult, 2004. My Sister's Keeper. https://en.wikipedia.org/wiki/My_Sister%27s_Keeper_(novel)
- Isaacson, 2001. The Code Breaker: Jennifer Doudna, Gene Editing, and the Future of the Human Race. https://en.wikipedia.org/wiki/The_Code_Breaker

Course outline:

Session/ date	Topic
#1	Introduction • Historical context • Current socio-ethical challenges • Scientific background Activity – introductions and discussion
#2	Genomics in reproduction #1 **Pre-implantation testing** • Pre-implantation genetic testing of in-vitro embryos • Polygenic Risk Score screening Activity – What conditions should we test for?
#3	Biobanks and genomic research and health disparities Genetic testing in the clinic Activity – role play
#4	Genomics in reproduction #2 Donor conception & the meaning of genetic relatedness Activity – debate **Mitochondrial Replacement**
#5	Genomics in reproduction #3 **Non-Invasive Prenatal testing**
	Newborn Screening and the BabySeq Project Activity – would you enroll in the BabySeq Project?
#6	Socio-ethical implications for low-cost whole genome sequencing
	Direct to Consumer genetic testing Activity – would you do DTC testing?
#7	Genomics and the future of human reproduction Germline gene editing using CRISPR Concluding activity: Considering all we have learned, what does genetic information & genetic relatedness mean for each of us?

Module 1 – Introduction

- **Historical context, current socio-ethical challenges, scientific background**

This introductory class will present the syllabus and then delve into some of the contexts in which genomics plays a role in medicine, research, and society. We will explore the historical roots of genomics in the ethical disasters generated by state-sponsored eugenics programs in the first half of the 20th Century. We will then consider the resulting ethical norms that govern the use of genomics today. We will also explore the cultural contexts in which genomics is understood (by discussing notions such as genetic reductionism, determinism, and exceptionalism); why genes have become cultural icons; and the hype surrounding genetic discoveries.

We will then examine what genomics is. Our understanding of genes, and our use of genetic information, has changed radically since the launch of the Human Genome Project in 1990. We have gone from the hope of single genes causing single common disorders to the reality of pleiotropy and polygenicity. To discuss the ethical issues in genomics one needs to understand the steps by which human genomic data are generated, including sequencing, mapping, variant calling, annotation, and interpretation. In addition, one needs to appreciate the technical, scientific, and clinical limitations that lead to uncertainty in genomic information and how that data is used.

Reading Materials for Module 1:

1. **Universal Declaration on the Human Genome and Human Rights**. 1997. United Nations Educational, Scientific and Cultural Organization (UNESCO), General Assembly, 29th Link to an external site
2. **Harm, hype, and evidence: ELSI research and policy guidance**. Caulfield T, Condit C. *Genome medicine*. 2013 Mar 26;5(3):21. Link to an external site
3. **Science and the sources of hype**. Caulfield T, Condit C. *Public Health Genomics*. 2012;15(3-4):209-17. Link
4. **Strategic vision for improving human health at The Forefront of Genomics**. Eric Green et al. *Nature*, 2020. 586: 683-692 – accessible here: https://pmc.ncbi.nlm.nih.gov/articles/PMC7869889/

Module 2 – Genomics in reproduction #1

- **Genomics in reproduction: Pre-implantation genetic testing of in-vitro embryos**
- **Polygenic Risk Score screening**

Class activity: What conditions should we test for?

Preimplantation genetic testing (PGT) of in-vitro embryos conceived through in-vitro fertilization (IVF) allows prospective parents to select which embryo to implant based on genetic information about disease-causing mutations, but potentially also based on traits, such as sex or certain physical attributes. Since this is done prior to pregnancy, such selection does not require termination, but PGT does raise the ethical challenges associated with justifying such selection and pits disability rights advocates , who think that selecting against disabling traits is an ethical mistake, against enthusiasts about testing who argue that we have an ethical duty to produce "the best possible child".

When targeting serious early-onset untreatable diseases, the use of PGT is relatively uncontroversial (notwithstanding objections related to the moral status of embryos). But when done for the purposes of enhancement or selection of non-medical traits, PGT raises numerous ethical concerns, at the individual level of parent-child relationships as well as the societal level of eugenics and disability rights. This class will describe the clinical and technical aspects of PGT and delve into the ethical and social debates surrounding the selection of future persons based on genetic information.

We will also explore prenatal testing, i.e., testing the fetus once the pregnancy has begun. It is now possible to conduct GS even earlier (12-16 weeks gestation), prenatally, on cells from chorionic villus sampling or amniocentesis, and in the future, it may be possible to perform GS as early as 8 weeks gestation on cell-free fetal DNA from maternal blood by NIPT (Non-Invasive Prenatal Testing). These methods could provide prospective parents with their fetus's complete GS.

While we live in a culture that assumes "knowledge is power", a vast amount of genetic information about (future) children raises ethical and social challenges. What genomic information should medical professionals provide to pregnant women and based on what criteria? What should be considered actionable and why? Should they move in the ACMG direction, and place limits on the amount of information that pregnant women receive, or should they move in the DTC direction, and provide whatever genomic data patients say they want? What role should the child's right to an open future and to privacy play? What societal concerns are raised by a possible future in which all individuals have been sequenced as fetuses or babies? What are the implications for "disability rights"?

Reading/Viewing Materials for Module 2

1. **The Disability Rights Critique of Prenatal Genetic Testing – Reflections and Recommendations.** Parens and Asch. 1999. *A Special Supplement to the Hastings Center Report*, 29:S2
2. **Procreative Beneficence: Why We Should Select the Best Children**. Savulescu, Julian (2001) *Bioethics* 15 (5/6): 413-26. Link Download Link
3. **Polygenic risk scores and embryonic screening: considerations for regulation.** Haining CM, Savulescu J, Keogh L, Schaefer GO. *J Med Ethics*. 2024 Dec 16 - https://jme.bmj.com/content/early/2024/12/16/jme-2024-110145
4. **Polygenic risk score for embryo selection-not ready for prime time**. Polyakov A, Amor DJ, Savulescu J, Gyngell C, Georgiou EX, Ross V, Mizrachi Y, Rozen G. *Hum Reprod*. 2022 Sep 30;37(10):2229-2236. https://pubmed.ncbi.nlm.nih.gov/35852518/
5. **Watch Prior to class: Gattaca** Link to Wikipedia page. The film can be streamed via Amazon Prime, Hulu, Sling TV, Star, Philo, or Vudu.

Additional elective readings for Module 2

1. **Disability and Genetics: A Disability Critique of Pre-natal Testing and Pre-implantation Genetic Diagnosis (PGD)**. Asch, Adrienne; and Barlevy, Dorit (May 2012) In: *eLS*. John Wiley Sons, Ltd: Chichester. Link Download Link
2. **Pre-implantation Genetic Diagnosis (PGD): The Road Forward in Canada**. Vardit Ravitsky, Minh Thu Nguyen, Stanislav Birko, Erika Kleiderman, Anne Marie Laberge, Bartha Maria Knoppers. *Canadian Journal of Obstetrics and Gynecology*. 41 (1): 68-71. January 2019. Link to an external site

1. **Deaf Culture, Cochlear Implants, and Elective Disability**. Tucker, Bonnie Poitras. 1998. *Hastings Center Report* 28, (4): 6-14. Link to an external site
2. **Having a perfect child.** Boehm. 2007. *Obstetrics and Gynecology,* 109(2): Part 1: 444-445. Link to an external site
3. **Notes From a Dragon Mom – mothering a child with Tay Sachs**. Rapp E. 2011. *New York Time* http://www.nytimes.com/2011/10/16/opinion/sunday/notes-from-a-dragon-mom.html?_r=1
4. **Made-to-Order Embryos for Sale – A Brave New World?** Cohen & Adashi. 2013. *New England Journal of Medicine* 368: 2517-2519. Link

Module 3

- **Biobanks and genomic research and health disparities**
- **Genetic testing in the clinic**
  Class activity: role play

Biobanks and genomic research and health disparities

The research landscape in genetics and genomics has changed dramatically over the past 2 decades, from primary studies of single disorders to the enrollment of patients into large biobanks where their genetic material is available for a myriad of research studies. The commitment to informed consent remains firmly in place, but how to achieve it becomes harder to conceptualize. Because researchers now need to share data with each other, they now ask patients (and/or research subjects) for "broad consent" to share their specimens and data, which usually includes their electronic health record data and are usually de-identified. But how is it possible to achieve truly informed consent to share data when so little is currently understood about what the data mean? How should large-scale research using biobanks approach secondary findings and the return of these results, when the researcher is no longer, or never was, in contact with the participant and the data is anonymous to the researcher? Finally, racial and ethnic minority populations continue to be under-represented in genomic research, impacting the understanding of genomic variants in these populations, and thereby limiting the equitable use of genomic information for clinical care. However, there are significant ethical, legal, and social implications for minority communities, including mistrust and privacy concerns, reinforced by historical abuses, including the Tuskegee syphilis experiment and well-publicized events such as development of the HeLa cell line from Henrietta Lacks.

Reading Materials for Module 3 Biobanks and genomic research and health disparities

1. **From "personalized" to "precision" medicine: the ethical and social implications of rhetorical reform in genomic medicine**. Juengst, J et al. *Hastings Center Report*. 2016. 46(5): 21-33. Link to an external site
2. **Informed consent for biobanking: consensus-based guidelines for adequate comprehension.** Beskow LM, Dombeck CB, Thompson CP, Watson-Ormond JK, Weinfurt KP. *Genet Med.* 2015;17(3):226-233. Link to an external site
3. **Defining and pursuing diversity in human genetic studies** Raven-Adams MC et al. *Nat Genet*. 2024 Oct;56(10):1985-1988. https://pubmed.ncbi.nlm.nih.gov/39251787/
4. I**f "race" is the answer, what is the question?—on "race," racism, and health: a social epidemiologist's perspective**, Nancy Krieger, 2006, *Social Science Research Council*, http://raceandgenomics.ssrc.org/Krieger/ (Links to an external site.)

Additional elective readings for Module 3 Biobanks and genomic research

- **Envisioning a More Just Genomics:** *Hastings Center Report*: Volume 54, Issue S2 - https://onlinelibrary.wiley.com/toc/1552146x/2024/54/S2
- **Broad consent for biobanks is best - provided it is also deep.** Mikkelsen RB, Gjerris M, Waldemar G, Sandøe P. *BMC Med Ethics*. 2019 Oct 15;20(1):71. https://pubmed.ncbi.nlm.nih.gov/31615491/
- **Researchers Need to Rethink and Justify How and Why Race, Ethnicity, and Ancestry Labels Are Used in Genetics and Genomics Research, Says New Report, News Release** | March 14, 2023 https://www.nationalacademies.org/news/2023/03/researchers-need-to-rethink-and-justify-how-and-why-race-ethnicity-and-ancestry-labels-are-used-in-genetics-and-genomics-

research-says-new-report#:~:text=The%20report%20says%20researchers%20should,misleading%2C%20inaccurate%2C%20and%20harmful

- **Maximizing the Value of Human Biospecimens: Lessons from Coronavirus and the Seattle Flu Study**. Wendler D and Berkman BE. *Am J Med Genet A.* 2020. Link to an external site
- **"Early Detection of Covid-19 through a Citywide Pandemic Surveillance Platform,"** Chu, H. Y., et al., *New England Journal of Medicine*, [published online ahead of print May 1, 2020]. Link to an external site
- **"Post-Consultation Decision: American Indian and Alaska Native (AI/AN) Inclusion in the All of Us Research Program COVID-19 Serology Study,"** National Institutes of Health. Link to an external site
- **The past, present, and future of the debate over return of research results and incidental findings.** Wolf SM. Genet Med. 2012 Apr;14(4):355-7. doi: 10.1038/gim.2012.26. No abstract available. Erratum in: Genet Med. 2012 Jun; 14(6): 630. PMID: 22481182. Link to an external site
- **Public Attitudes toward Consent and Data Sharing in Biobank Research: A Large Multi-site Experimental Survey in the US.** Sanderson SC, Brothers KB, Mercaldo ND, et al. *Am J Hum Genet.* 2017;100(3):414-427. doi: 410.1016/j.ajhg.2017.1001.1021. Epub 2017 Feb 1019. Link to an external site
- The Oxford Handbook of Public Health Ethics, ed. A. C. Mastroianni, J. P. Kahn, and N. E. Kass (New York: Oxford University, 2019). Link to an external site
    - Taylor, H. A., "**Framing Public Health Research Ethics**," 331-341
    - Lee, L. M., "**Public Health Surveillance: Ethical Considerations**," 320-330
    - Smith, M. and R. Upshur, "**Pandemic Disease, Public Health, and Ethics**," 797-811
- **How Not to Talk About Race and Genetics**. March 30, 2018 https://www.buzzfeednews.com/article/bfopinion/race-genetics-david-reich (Links to an external site.)

Genetic testing in the clinic

Genomic sequencing (GS) is increasingly being performed to diagnose rare disorders, individualize cancer treatments, and inform drug selection and dosing (pharmacogenomics), and is expanding to carrier status and prenatal testing, and potentially screening for disease risk. This is the promise of genomic medicine: using genomic information to inform patient care. One consequence of GS is the discovery of secondary findings, unrelated to the primary indication for GS, which indicate that the patient has a "medically actionable" (preventable and/or treatable) condition. As GS becomes integrated into medical care, the unexpected identification of these variants associated with, or known to cause, such conditions is becoming more common. Although identifying an unsuspected medically actionable condition enhances the ability of health care providers to intervene to prevent disease, often such findings are unsolicited, i.e., unrelated to the indication for sequencing or the patient's health concerns, and in some cases not ordered by the provider receiving the result.

To provide guidance to laboratories conducting GS, and to clinicians ordering GS for their patients, the American College of Medical Genetics and Genomics (AMCG) developed guidelines for laboratories on the return of highly actionable "secondary" (initially called "incidental") genetic findings that arise in the course of GS for a primary indication, which in the initial document was mandatory. This publication was very controversial as it brought up the tension between patient autonomy and medical beneficence (or, some would charge, "paternalism"), as a panel of genetics experts decided which genomic variants were

actionable enough to warrant returning to patients without considering if patients wanted these results. Even if a patient might think that she had an autonomy-based right to not learn about these findings, this panel initially decided that autonomy would not prevail in this context and that any findings from the list of actionable genes would be returned regardless of the patient's preference. In response to the pushback against the original guidelines that required return of these findings, however, the ACMG eventually came out with updated guidelines, giving individuals a choice about getting secondary findings.

Disclosure of results to patients also creates ethical tensions between patient autonomy and medical beneficence, related to possible impact in family members. Genetic information can have health implications for those genetically related to the patient. When patients prefer not to disclose actionable information to relatives, clinicians may find themselves caught between their obligation to respect patient confidentiality and their duty to warn others. How should clinicians balance privacy and HIPAA (Health Insurance Portability and Accountability Act), the USA legislation providing data privacy and security provisions to safeguarding medical information, with informing family members of their risk?

Reading Materials for Module 3 Genetic testing in the clinic

1. **ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing.** Green RC, Berg JS, Grody WW, Kalia SS, Korf BR, Martin CL, McGuire AL, Nussbaum RL, O'Daniel JM, Ormond KE, Rehm HL, Watson MS, Williams MS, Biesecker LG; American College of Medical Genetics and Genomics. Genet Med. 2013 Jul;15(7):565-74. Link to an external site
2. **Point-counterpoint. Ethics and genomic incidental findings.** McGuire AL, Joffe S, Koenig BA, Biesecker BB, McCullough LB, Blumenthal-Barby JS, Caulfield T, Terry SF, Green RC. Science. 2013 May 31;340(6136):1047-8. Link to an external site
3. **Point-counterpoint. Patient autonomy and incidental findings in clinical genomics.** Wolf SM, Annas GJ, Elias S. Science. 2013 May 31;340(6136):1049-50. Link to an external site

Additional elective readings for Module 3 Genetic testing in the clinic

1. **Making Sense of the Genome Remains a Work in Progress.** Wylie Burke. JAMA September 25, 2018; 320(12): 1247-48. LinkLinks to an external site.
2. **Genetic Links, Family Ties, and Social Bonds: Rights and Responsibilities in the Face of Genetic Knowledge**. Rhodes, Rosamond. 1998. *Journal of Medicine and Philosophy* 23, No. 1: 10-30. Link to an external site
1. **Disclosing Genetic Information to Family Members: The Role of Empirical Ethics**. Dupras Charles & Ravitsky Vardit**.** In: *eLS* 2013, John Wiley & Sons Ltd: Chichester Link (Links to an external site.)
2. **Do your family members have a right to your genetic code?** Link to an external site

Module 4 – Genomics in reproduction #2

- **Donor conception and the meaning of genetic relatedness**
- **Mitochondrial Replacement**

Class activity: debate

For many people, genetic relatedness plays a crucial role in identity and relationship formation. For example, prospective parents' desire for genetically related children underlies the multi-billion infertility treatment industry. But what happens when the assistance of third-party DNA is required for conception? Today, sperm and egg donation is often used in fertility treatment, resulting in hundreds of thousands of donor-conceived individuals world-wide. While in the past, donor conception was usually kept secret, research and decades of experience have led to the recommendation to tell children the truth about the circumstances of their conception. Yet, in many countries, donor anonymity is still the norm, and many parents still keep this information secret.

Gamete donation is thus a vast 'social experiment' regarding the role and meaning of genetic relatedness. Why do many donor-conceived individuals argue that they have a right to know the identity of their donor? What do donors and parents want? How is gamete donation similar to and/or different from adoption? How do various legal systems approach tensions surrounding donor conception? For example, should donor conception be noted on birth certificates? This class will explore the vibrant bioethical debate on gamete donation, donor anonymity, and the alleged right to know one's genetic origins.

Reading Materials for Module 4

1. **'Knowing where you come from': The rights of donor-conceived individuals and the meaning of genetic relatedness**. Ravitsky**.** Minnesota Journal of Law Science & Technology, 11(2): 655-684. Link to an external site
2. **Conceived and Deceived: The Medical Interests of Donor-Conceived Individuals**. Ravitsky Vardit. Hastings Center Report, 42 (1): 17-22. 2012. Link to an external site
3. **Is There a Right to Know One's Genetic Origins?** De Melo Martin, I. 2014. Hastings Center Report 44(2): 28-35. Link to an external site
4. **Autonomous Choice and the Right to Know One's Genetic Origins**. Ravitsky, V. 2014. Hastings Center Report 44(2): 36-37. Link
5. **Mitochondrial/Nuclear Transfer: A Literature Review of the Ethical, Legal and Social Issues**. Dupras-Leduc Raphaëlle, Stanislav Birko & Vardit Ravitsky. *Canadian Journal of Bioethics*. 1 (2): 1-17. 2018.

Additional elective readings for Module 4

1. **Gamete donation and anonymity: disclosure to children conceived with donor gametes should not be optional**. McGee, Brakman and Gurmankin. 2001. Link to an external site
2. **Disclosure to children conceived with donor gametes should be optional**. Patrizio, Mastroianni and Mastroianni. 2001. Human Reproduction, 16(10): 2036-8. Link to an external site

Module 5 – Genomics in reproduction #3

- **Non-Invasive Prenatal testing**
- **Newborn Screening and the BabySeq Project**

Class activity: would you enroll in BabySeq?

Non-Invasive Prenatal testing

We will also explore prenatal testing, i.e., testing the fetus once the pregnancy has begun. It is now possible to conduct GS even earlier (12-16 weeks gestation), prenatally, on cells from chorionic villus sampling or amniocentesis, and in the future, it may be possible to perform GS as early as 8 weeks gestation on cell-free fetal DNA from maternal blood by NIPT (Non-Invasive Prenatal Testing). These methods could provide prospective parents with their fetus's complete GS.

While we live in a culture that assumes "knowledge is power", a vast amount of genetic information about (future) children raises ethical and social challenges. What genomic information should medical professionals provide to pregnant women and based on what criteria? What should be considered actionable and why? Should they move in the ACMG direction, and place limits on the amount of information that pregnant women receive, or should they move in the DTC direction, and provide whatever genomic data patients say they want? What role should the child's right to an open future and to privacy play? What societal concerns are raised by a possible future in which all individuals have been sequenced as fetuses or babies? What are the implications for "disability rights"?

Reading/Viewing Materials for Module 5 Non-invasive prenatal testing

5. **NIPT for Aneuploidy and Beyond: Challenges of Responsible Innovation in Prenatal Screening**. Dondrop et al. 2015. European Journal of Human Genetics, 1-13. Link to an external site
6. **The Shifting Landscape of Prenatal Testing: Between Reproductive Autonomy and Public Health**. Vardit Ravitsky. Hastings Center Report, 47 (6): S34-S40. Nov-Dec 2017. Link to an external site
7. **Moving Towards Routine Non-Invasive Prenatal Testing (NIPT): Challenges Related to Women's Autonomy**. Stanislav Birko, Marie-Eve Lemoine, Minh Thu Nguyen & Vardit Ravitsky**.***OBM Genetics*, 2 (2): 1-14. April 20, 2018.

Additional elective readings for Module 5 Non-invasive prenatal testing

1. **Providing unrestricted access to prenatal testing does not translate to enhanced autonomy**. Ravitsky Vardit, François Rousseau, Anne-Marie Laberge. *American Journal of Bioethics*, 17 (1): 39-41. 2017.
2. **The emergence and global spread of non-Invasive Prenatal Testing**. Vardit Ravitsky & Marie-Christine Roy** (both are first authors), Hazar Haidar, Lidewij Henneman, John Marshall, Ainsley J. Newson, Olivia M.Y. Ngan, Tamar Nov-Klaiman. *Annual Review of Genomics and Human Genetics*, 22(1), 309-338, 2021.
3. **When They Warn of Rare Disorders, These Prenatal Tests Are Usually Wrong**. By Sarah Kliff and Aatish Bhatia. New York Times. Jan. 1, 2022. https://www.nytimes.com/2022/01/01/upshot/pregnancy-birth-genetic-testing.html - Associated podcast: "Investigating the Prenatal Testing Market". The Daily Podcast. New York Times. https://www.nytimes.com/2022/01/04/podcasts/the-daily/prenatal-tests-pregnancy-birth.html?rref=vanity

Reactions to the article:

4. "What The NYTimes Got Wrong On Prenatal Screening", Ellen Matloff, Forbes. https://www.forbes.com/sites/ellenmatloff/2022/01/06/what-the-nytimes-got-wrong-on-prenatal-screening/?sh=3e12eb4237a7
5. "The Questions We Should Really Be Asking After Reading the NY Times Article About Prenatal cfDNA Screening For Microdeletions", Robert Resta, The DNA Exchange. https://thednaexchange.com/2022/01/08/the-questions-we-should-really-be-asking-after-reading-the-ny-times-article-about-prenatal-cfdna-screening-for-microdeletions/
6. "The tragedy of eugenics and the babies not born". Father Raymond J. de Souza. National Post. https://nationalpost.com/opinion/raymond-j-de-souza-the-tragedy-of-eugenics-and-the-babies-not-born

Newborn Screening and the BabySeq Project

Rapid Genomic sequencing (GS) as a clinical test is now being performed on newborns with multiple congenital anomalies to make a diagnosis as soon as possible, avoiding a long and drawn out "diagnostic odyssey". Thus, the technology, at an increasingly lower cost, is available for the possibility of incorporating GS into the mandated newborn screening (NBS) of all babies, including healthy ones. As NIH director Francis Collins has said: "…whether you like it or not, a complete sequencing of newborns is not far away".

The most commonly cited criteria for conventional NBS insist that newborn screening tests should have high sensitivity/specificity, for conditions where the natural history is well understood, and where there are available and efficacious treatments. Efforts to broaden the NBS mandate, or even to implement clinical genetic testing of older children have often been resisted, under the assumption that genetic risk information was uncertain and upsetting, that it could damage the parent-child bond, create "patients in waiting" among children and foreclose the child's choice of whether to seek this information as an adult.

Traditionally, bioethicists have agreed that, out of respect for a child's "right to an open future," children should not be genetically tested, unless the discovery of a positive result could lead to medical intervention. This notion is now coming under increasing pressure, from several angles. For one thing, the more that we study how children make decisions, the more we understand that at least some of them have the capacity to make informed decisions well before the age of majority. More importantly, some people are arguing that the older model erroneously conceives of children in terms that are too individualistic and atomistic—and that this model fails to recognize that children live in families, and that what is good for families is ultimately good for the children who are part of them. Moreover, this opens the way for parents to use testing results from their children to, e.g., consider in their own future reproductive planning.

Reading Materials for Module 5 Newborn Screening and the BabySeq Project

1. **Professionally Responsible Disclosure of Genomic Sequencing Results in Pediatric Practice.** McCullough LB, Brothers KB, Chung WK, Joffe S, Koenig BA, Wilfond B, Yu JH; Clinical Sequencing Exploratory Research (CSER) Consortium Pediatrics Working Group. Pediatrics. 2015 Oct; 136(4): e974-82. Link to an external site
2. **Mandatory extended searches in all genome sequencing: "incidental findings," patient autonomy, and shared decision making.** Ross LF, Rothstein MA, Clayton, JAMA. 2013 Jul 24;310(4):367-8. Link to an external site

3. **Predictive genetic testing of children and the role of the best interest standard.** Ross LF. J Law Med Ethics**.** 2013 Winter; 41(4): 899-906. Link to an external site
4. **Disclosing Secondary Findings from Pediatric Sequencing to Families: Considering the "Benefit to Families".** Wilfond BS, Fernandez CV, Green RC. J Law Med Ethics. 2015 Fall; 43(3): 552-8. Link to an external site

Additional elective readings for Module 5 Newborn Screening and the BabySeq Project

- **Genomic newborn screening: public health policy considerations and recommendations.** Friedman JM, Cornel MC, Goldenberg AJ, Lister KJ, Sénécal K, Vears DF; Global Alliance for Genomics and Health Regulatory and Ethics Working Group Pediatric Task Team. *BMC Med Genomics*. 2017 Feb 21;10(1):9. Link to an external site
- **The BabySeq Project: A clinical trial of genome sequencing in a diverse cohort of infants**. Smith HS et al. *Am J Hum Genet*. 2024 Oct 3;111(10):2094-2106. https://pubmed.ncbi.nlm.nih.gov/39288765/
- **Genomic sequencing in newborn screening: balancing consent with the right of the asymptomatic at-risk child to be found.** Knoppers BM, Bonilha AE, Laberge AM, Ahmed A, Newson AJ. *Eur J Hum Genet*. 2024 Aug 12. doi: 10.1038/s41431-024-01677-w. Epub ahead of print. PMID: 39134767. https://pubmed.ncbi.nlm.nih.gov/39134767/
- **DNA Sequencing in Newborn Screening: Opportunities, Challenges, and Future Directions.** Jeanne M, Chung WK. *Clin Chem*. 2025 Jan 3;71(1):77-86. https://pubmed.ncbi.nlm.nih.gov/39749512/
- **Are Parents Really Obligated to Learn as Much as Possible about Their Children's Genomes?** Johnston J, Juengst E. *Hastings Cent Rep*. 2018 Jul;48 Suppl 2(Suppl 2):S14-S15. https://pubmed.ncbi.nlm.nih.gov/30133729/

Module 6

- **Socio-ethical Implications for low-cost whole genome sequencing**
- **Direct-to-Consumer (DTC) genetic testing**

Class activity: would you do DTC testing?

Socio-ethical Implications for low-cost whole genome sequencing

Reading Materials for Module 6 Socio-ethical Implications for low-cost whole genome sequencing

1. **Ethical Considerations in Research with Genomic Data**, Rachel Horton & Anneke Lucassen (2023), *The New Bioethics*,29:1, 37-51, https://www.tandfonline.com/doi/full/10.1080/20502877.2022.2060590
2. **Genomic newborn screening: Are we entering a new era of screening?** Spiekerkoetter U, Bick D, Scott R, Hopkins H, Krones T, Gross ES, Bonham JR. *J Inherit Metab Dis*. 2023 Sep;46(5):778-795. https://onlinelibrary.wiley.com/doi/full/10.1002/jimd.12650
3. **Opportunities and challenges for the computational interpretation of rare variation in clinically important genes,** McInnes G, Sharo AG, Koleske ML, Brown JEH, Norstad M, Adhikari AN, Wang S, Brenner SE, Halpern J, Koenig BA, Magnus DC, Gallagher RC, Giacomini KM, Altman RB. *Am J Hum Genet*. 2021 Apr 1;108(4):535-548. **https://pubmed.ncbi.nlm.nih.gov/33798442/**

Additional elective readings for Module 6 Socio-ethical Implications for low-cost whole genome sequencing

1. **Understanding DNA Ancestry (Understanding Life),** Sheldon Krimsky https://www.amazon.com/Understanding-DNA-Ancestry-Life/dp/1108816037/ref=tmm_pap_swatch_0?_encoding=UTF8&qid=&sr= (for purchase through Amazon)

Direct to Consumer genetic testing

Direct-to-consumer (DTC) sales of genetic testing for ancestry are booming. Millions of people choose to pay for this type of 'recreational genomics' and are fascinated by the results companies provide about their origins and potentially about unknown family relatives. But these tests are often not innocuous. They carry various risks, from concerns about privacy violations to psychological harm caused by revelations about genetic origins, family secrets, and painful pasts.
This class will explain the science of ancestry testing and its limitations. It will then delve into the rich bioethical debates surrounding these tests, using case studies that illustrate the impact such testing can have on individuals and families. It will also highlight the ways in which DTC reinforces certain cultural perspectives regarding the role genomics play in identity formation.

Reading Materials for Module 6 Direct to Consumer genetic testing

1. **Direct to consumer genetic testing-is all knowledge power**? Margaret McCartney. *BMJ* 2015 Jan 26;350. Link to an external site
2. **How Well Do Customers of Direct-to-Consumer Personal Genomic Testing Services Comprehend Genetic Test Results? Findings from the Impact of Personal Genomics Study**. Ostergren JE, Gornick MC, Carere DA, Kalia SS, Uhlmann WR, Ruffin MT, Mountain JL, Green RC, Roberts JS; PGen Study Group. *Public Health Genomics*. 2015;18(4):216-24. Link to an external site
3. **Direct-to-consumer genomics on the scales of autonomy**. Vayena E. *Journal of Medical Ethics*. 2015 Apr; 41(4): 310-4. Link to an external site

4. **Privacy, autonomy and direct-to-consumer genetic testing: a response to Vayena** Kyle van Oosterum

Additional elective readings for Module 6 Direct to Consumer genetic testing

1. **Consuming Genomes**. Curnutte and Testa. *New Genetics and Society*, vol 31(2) 2012. Link
2. **Why your DNA test won't reveal the real you**. TIMOTHY CAULFIELD. MAY 2, 2018. Link to an external site
3. **How Not to Talk About Race and Genetics**. March 30, 2018. Link
4. **NYT** https://www.nytimes.com/2021/12/27/magazine/dna-test-crime-identification-genome.html
5. **Book:** https://www.cambridge.org/core/books/consumer-genetic-technologies/FB376A78995901CF3C761F34105242E8

Module 7

Genomics and the future of human reproduction: Germline gene editing using CRISPR

- **Course wrap up**

Concluding activity: Considering all we have learned, what does genetic information & genetic relatedness mean for each of us?

Inspired by the advent of recombinant DNA technology and the promise of human gene therapy, germline modification has been the subject of active discussion for over half a century. At the heart of this discussion is a concern about intentionally introducing modification into the human genome that would be inherited by future generations. Recently, the discovery of CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) has come to rule the social and ethical debate about 'crossing the germline barrier'.

There is overwhelming consensus that CRISPR technology used for somatic gene editing will usher in an age of cheap and easy genetic manipulation, may provide life-long cures for diseases with a single treatment, and brings new therapies to clinic, for example for sickle cell disease. However, CRISPR gene editing of germline cells (introducing genetic modifications into embryos, eggs, or sperm) could be passed on to descendants and is a tremendously contentious issue.

Reports and policy statements have voiced numerous ethical and social concerns, such as the unknown risks that could potentially impact future generations and the course of human evolution; the cost of these interventions making them accessible only to the rich and consequently exacerbating social gaps; or the use of gene editing for purposes of enhancement, rather than prevention or treatment of disease in ways that promote eugenic social attitudes. Due to the controversial nature of germline editing, all published and issued statements addressing policy and governance mention the need for public debate, engagement, consultation, or education regarding the possible uses, limitations, and appropriate regulation of this technology.

Policy regarding germline gene editing varies globally, with approaches ranging from restrictive, frequently accompanied by criminal sanctions, to intermediate or more permissive. The use of genetically-edited human embryos or germs cells for reproductive purposes, i.e. to initiate a pregnancy, is forbidden throughout the world at this time. Yet, in November 2018 the world was shocked to learn of the birth of the first genetically-edits twins in China.

This class will explain the science of CRISPR, the ethical debate surrounding it, and various policy approaches. It will delve into the global scandal that erupted with the birth of the first edited babies was announced and explore 'what went wrong' in the case of this experiment.

Reading Materials for Module 7

1. **Adopt a moratorium on heritable genome editing.** Lander et al. Nature 567, 165-168 (2019). Link to an external site
2. **The 'serious' factor in germline modification.** Journal of Medical Ethics. Erika Kleiderman, Vardit Ravitsky & Bartha Maria Knoppers. 20 July 2019. Link to an external site
3. **How bans on germline editing deprive patients with mitochondrial disease**. I. Glenn Cohen, Eli Y. Adashi & Vardit Ravitsky. *Nature Biotechnology* 37: 589-592, 2019.

Viewing Materials for Module 7

1. **The Science: What is CRISPR**? (7 mins) Link (Links to an external site.)

2. **An application: How Gene Editing Is Curing Disease**. (13 mins) Link (Links to an external site.)
3. **Ethical and social issues: CRISPR: What is the future of gene editing**? (8 mins) Link (Links to an external site.)

Additional elective readings for Module 7

1. **Rewriting the genetic bond: Gene editing and our understanding of genetic parenthood**. *Bioethics***.** Shelly Simana and Vardit Ravitsky**.** 2022 Nov 9.
2. **Human Nature**: In Conversation with Nobel Prize Winner Jennifer Doudna. (1 hr) Link
3. Unnatural Selection – Netflix documentary series. Link to wikipedia page. (Links to an external site.) Please watch the series on Netflix.
4. **CRISPR in the North American popular press.** Alessandro Marcon, Zubin Master, Vardit Ravitsky, & Timothy Caulfield. *Genetics in Medicine*. 21 : 2184–2189. 2019 Link to an external site
5. **The Regulation of Mitochondrial Replacement Therapy, Around the World.** I. Glenn Cohen, Eli Y. Adashi, Sara Gerke, César Palacios-González & **Vardit Ravitsky**. *Annual Review of Genomics and Human Genetics*. 21 (3): 3.1–3.22, 2020.
6. **The "three-parent baby": A case study of how language frames the ethical debate regarding an emerging technology**. Ravitsky Vardit, Birko Stanislav & Dupras-Leduc Raphaelle. *American Journal of Bioethics* 15 (12): 57-60. 2015.